$%^Dialog;HighlightOn=%%%;HighlightOff=%%%;

Logging in to Dialog

Trying 31060000009999...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
****
ENTER PASSWORD:
****
Welcome to DIALOG

Dialog level 02.03.27D

Last logoff: 09apr02 09:03:54
Logon file405 09apr02 09:04:16
*
SYSTEM:HOME
Cost is in DialUnits
Menu System II: D2 version 1.7.8 term=ASCII
*** DIALOG HOMEBASE(SM) Main Menu ***

Information:
1. Announcements (new files, reloads, etc.)
2. Database, Rates, & Command Descriptions
3. Help in Choosing Databases for Your Topic
4. Customer Services (telephone assistance, training, seminars, etc.)
5. Product Descriptions

Connections:
6. DIALOG(R) Document Delivery
7. Data Star(R)

/H = Help /L = Logoff /NOMENU = Command Mode

Enter an option number to view information or to connect to an online service. Enter a BEGIN command plus a file number to search a database (e.g., B1 for ERIC).
? dialog
>>Invalid Option Number

*** DIALOG HOMEBASE(SM) Main Menu ***

Information:
1. Announcements (new files, reloads, etc.)
2. Database, Rates, & Command Descriptions
3. Help in Choosing Databases for Your Topic
4. Customer Services (telephone assistance, training, seminars, etc.)
5. Product Descriptions

Connections:
6. DIALOG(R) Document Delivery
7. Data Star(R)

/H = Help /L = Logoff /NOMENU = Command Mode

Enter an option number to view information or to connect to an online service. Enter a BEGIN command plus a file number to search a database (e.g., B1 for ERIC).
? b 410

09apr02 09:04:18 User226352 Session D618.1
$0.00 0.217 DialUnits FileHomeBase
$0.00 Estimated cost FileHomeBase
$0.00 Estimated cost this search
$0.00 Estimated total session cost 0.217 DialUnits

File 410:Chronolog(R) 1981-2002/Feb
(c) 2002 The Dialog Corporation

Set Items Description
--- ----- -----------
? set hi %%%;set hi %%%
HILIGHT set on as '%%%'%%%
%%%HILIGHT set on as '%%%'
? biochem
>>>"IOCHEM" is not a valid category or service name
>>>No valid files specified
? b biochem
09apr02 09:04:23 User226352 Session D618.2
$0.00 0.144 DialUnits File410
$0.00 Estimated cost File410
$0.01 TELNET
$0.01 Estimated cost this search
$0.01 Estimated total session cost 0.361 DialUnits

SYSTEM:OS - DIALOG OneSearch
File 5:Biosis Previews(R) 1969-2002/Mar W5
(c) 2002 BIOSIS
File 6:NTIS 1964-2002/Apr W2
(c) 2002 NTIS, Intl Cpyrght All Rights Res
*File 6: See HELP CODES6 for a short list of the Subject Heading Codes (SC=, SH=) used in NTIS.
File 34:SciSearch(R) Cited Ref Sci 1990-2002/Apr W1
(c) 2002 Inst for Sci Info
File 40:Enviroline(R) 1975-2002/Mar
File 41:Pollution Abs 1970-2002/Apr
(c) 2002 Cambridge Scientific Abstracts
File 50:CAB Abstracts 1972-2002/Mar
(c) 2002 CAB International
*File 50: Truncating CC codes is recommended for full retrieval.
See Help News50 for details.
File 65:Inside Conferences 1993-2002/Mar W5
(c) 2002 BLDSC all rts. reserv.
File 68:Env.Bib. 1974-2002/Feb
(c) 2002 Internl Academy at Santa Barbara
File 71:ELSEVIER BIOBASE 1994-2002/Apr W1
(c) 2002 Elsevier Science B.V.
File 73:EMBASE 1974-2002/Mar W5
(c) 2002 Elsevier Science B.V.
*File 73: For information about Explode feature please
see Help News73.
File 76:Life Sciences Collection 1982-2002/Mar
(c) 2002 Cambridge Sci Abs
*File 76: UDs have been manually adjusted to reflect the current months data. There is no data missing.
File 77:Conference Papers Index 1973-2002/Mar
(c) 2002 Cambridge Sci Abs
File 94:JICST-EPlus 1985-2002/Feb W4
(c)2002 Japan Science and Tech Corp(JST)
*File 94: There is no data missing. UDs have been adjusted to reflect the current months data. See Help News94 for details.
File 98:General Sci Abs/Full-Text 1984-2002/Feb
(c) 2002 The HW Wilson Co.
File 103:Energy SciTec 1974-2002/Feb B1
(c) 2002 Contains copyrighted material
*File 103: For access restrictions, see HELP RESTRICT.
File 143:Biol. & Agric. Index 1983-2002/Feb
(c) 2002 The HW Wilson Co
File 144:Pascal 1973-2002/Apr W1
(c) 2002 INIST/CNRS
File 155:MEDLINE(R) 1966-2002/Mar W5
File 156:ToxFile 1966-2002/Feb W4
(c) 2002
File 162:CAB HEALTH 1983-2002/Feb
(c) 2002 CAB INTERNATIONAL
*File 162: Truncating CC codes is recommended for full retrieval.
See Help News162 for details.
File 172:EMBASE Alert 2002/Apr W1
(c) 2002 Elsevier Science B.V.
File 305:Analytical Abstracts 1980-2002/Mar W3
(c) 2002 Royal Soc Chemistry
*File 305: Frequency of updates and Alerts changing to weekly.
See HELP NEWS 305.
File 369:New Scientist 1994-2002/Mar W5
(c) 2002 Reed Business Information Ltd.

File 370:Science 1996-1999/Jul W3
(c) 1999 AAAS
*File 370: This file is closed (no updates). Use File 47 for more current information.
File 399:CA SEARCH(R) 1967-2002/UD=13615
(c) 2002 AMERICAN CHEMICAL SOCIETY
*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
(c) 1998 Inst for Sci Info

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   Set  Items  Description
   ---  -----  -----------
? s (scatter(w)factor? or tumor(w)cytotoxic(w)facor? or TCF or TCF(w)II)
Processed 10 of 26 files ...
Processing
Processed 20 of 26 files ...
Completed processing all files
         66626  SCATTER
       8293455  FACTOR?
          8960  SCATTER(W)FACTOR?
       3154219  TUMOR
        408968  CYTOTOXIC
           332  FACOR?
             0  TUMOR(W)CYTOTOXIC(W)FACOR?
          7351  TCF
          7351  TCF
       3387456  II
            17  TCF(W)II
     S1  16300  (SCATTER(W)FACTOR? OR TUMOR(W)CYTOTOXIC(W)FACOR? OR TCF
                 OR TCF(W)II)
? s s1 and sepsis and (treat? or prevent? or modulat? or reduc? or ameloriat?)
Processing
Processing
Processed 10 of 26 files ...
Processing
Processing
Processed 20 of 26 files ...
Processing
Completed processing all files
         16300  S1
        162479  SEPSIS
      11221311  TREAT?
       3134312  PREVENT?
       1287933  MODULAT?
       7122846  REDUC?
            78  AMELORIAT?
     S2     12  S1 AND SEPSIS AND (TREAT? OR PREVENT? OR MODULAT? OR
                 REDUC? OR AMELORIAT?)
? rd s2
...completed examining records
     S3     12  RD S2 (unique items)
? t s3/7/all
>>>Format 7 is not valid in file 143
```

3/7/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06343195 Genuine Article#: YK655 Number of References: 54
Title: Simultaneous or delayed administration of hepatocyte growth factor equally represses the fibrotic changes in murine lung injury induced by bleomycin - A morphologic study
Author(s): Yaekashiwa M (REPRINT) ; Nakayama S; Ohnuma K; Sakai T; Abe T;
Satoh K; Matsumoto K; Nakamura T; Takahashi T; Nukiwa T
Corporate Source: TOHOKU UNIV,INST DEV AGING & CANC, DIV CANC CONTROL, DEPT
RESP ONCOL & MOL MED/SENDAI/MIYAGI 98077/JAPAN/ (REPRINT); TOHOKU
UNIV,INST DEV AGING & CANC, DEPT PATHOL, DIV ORGAN
PATHOPHYSIOL/SENDAI/MIYAGI 98077/JAPAN/; OSAKA UNIV,SCH MED, BIOMED RES
CTR, DEPT ONCOL, DIV BIOCHEM/OSAKA 553//JAPAN/
Journal: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, 1997
, V156, N6 (DEC), P1937-1944
ISSN: 1073-449X Publication date: 19971200
Publisher: AMER LUNG ASSOC, 1740 BROADWAY, NEW YORK, NY 10019
Language: English Document Type: ARTICLE
Abstract: Hepatocyte growth factor (HGF) is a humoral mediator of epithelial-mesenchymal interactions, acting on a variety of epithelial cells as mitogen, motogen, and morphogen. Exogenous HGF acts as a hepatotrophic factor and a renotrophic factor during experimental injury. To investigate whether HGF has a pulmotrophic function, human recombinant HGF was administered to C57BL/6 mice with severe lung injury by bleomycin (BLM). Low dose simultaneous and continuous administration of HGF (50 mu g/mouse/7 d) with BLM (100 mg/mouse/7 d)
repressed fibrotic morphological changes at 2 and 4 wk. Ashcroft score showed a significant difference in lung fibrosis with and without HGF at 4 wk (3.7 +/- 0.4 versus 4.9 +/- 0.3, p < 0.05). Furthermore, either simultaneous or delayed administration of high dose HGF (280 mu g/mouse/14 d) equally repressed fibrotic changes by BLM when examined at 4 wk (Ashcroft score: 2.6 +/- 0.4 and 2.4 +/- 0.2 versus 4.1 +/- 0.2, p < 0.01). Hydroxyproline content in the lungs was significantly lower in mice with either simultaneous or delayed administration of high dose HGF as compared to those administered BLM alone (121.8 +/- 8.1% and 113.2 +/- 6.2% versus 162.7 +/- 4.6%, p < 0.001). These findings indicate that exogenous HGF acts as a pulmotrophic factor in vivo and %%%prevents%%% the progression of BLM-induced lung injury when
administered in either a simultaneous or delayed fashion. HGF may be a potent candidate to %%%prevent%%% or %%%treat%%% lung fibrosis.

3/7/2 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05852432 Genuine Article#: XB974 Number of References: 20
Title: Monocyte deactivation in septic patients: Restoration by IFN-gamma %%%treatment%%%
Author(s): Docke WD (REPRINT) ; Randow F; Syrbe U; Krausch D; Asadullah K;
Reinke P; Volk HD; Kox W
Corporate Source: HUMBOLDT UNIV BERLIN,INST MED IMMUNOL/D-10098
BERLIN//GERMANY/ (REPRINT); HUMBOLDT UNIV BERLIN,CLIN ANESTHESIOL &
INTENS CARE MED/D-10098 BERLIN//GERMANY/; HUMBOLDT UNIV BERLIN,VIRCHOW
CLIN, DEPT NEPHROL & INTERNAL INTENS CARE/D-13353 BERLIN//GERMANY/
Journal: NATURE MEDICINE, 1997, V3, N6 (JUN), P678-681
ISSN: 1078-8956 Publication date: 19970600
Publisher: NATURE PUBLISHING CO, 345 PARK AVE SOUTH, NEW YORK, NY
10010-1707
Language: English Document Type: ARTICLE
Abstract: Neutralization of proinflammatory cytokines, such as tumor necrosis factor-alpha. (TNF-alpha) or interleukin-1 (IL-1), decreases mortality in several animal models of %%%sepsis%%%. However, recent clinical trials did not show an unequivocal improvement in survival. In contrast to animals, which succumb to shock during the first 72 hours, we found that many patients die much later with signs of opportunistic infections accompanied by downregulation of their monocytic HLA-DR expression and %%%reduced%%% ability to produce lipopolysaccharide (LPS)-induced TNF-alpha in vitro(1-3). This phenomenon of monocyte deactivation in septic patients with fatal outcome shows similarities to experimental monocytic refractoriness induced by LPS desensitization or by pretreatment with its endogenous mediators IL-10 and transforming growth factor-beta (%%%TCF%%%-beta)(4). In order to strengthen their
antimicrobial defense, here we tested whether interferon-gamma (IFN-gamma) can improve monocytic functions in these patients and in experimental monocytic deactivation. The considerably lowered in vitro levels of LPS-induced TNF-alpha in these situations were significantly enhanced by IFN-gamma, but did not reach the extremely high levels of

IFN-gamma primed naive cells from healthy donors. Moreover, IFN-gamma
applied to septic patients with low monocytic HLA-DR expression restored the deficient HLA-DR expression and in vitro LPS-induced TNF-alpha secretion. Recovery of monocyte function resulted in clearance of %%%sepsis%%% in eight of nine patients. These data suggest
that IFN-gamma %%%treatment%%% in carefully selected septic patients is
a novel therapeutic strategy worth pursuing.

3/7/3 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05299649 Genuine Article#: VP226 Number of References: 46
Title: EXPRESSION OF TYPE-II NITRIC-OXIDE SYNTHASE IN PRIMARY HUMAN
ASTROCYTES AND MICROGLIA - ROLE OF IL-1-BETA AND IL-1 RECEPTOR
ANTAGONISTS
Author(s): LIU J; ZHAO ML; BROSNAN CF; LEE SC
Corporate Source: YESHIVA UNIV ALBERT EINSTEIN COLL MED,DEPT PATHOL
NEUROPATHOL F717N,1300 MORRIS PK AVE/BRONX//NY/10461; YESHIVA UNIV
ALBERT EINSTEIN COLL MED,DEPT PATHOL NEUROPATHOL F717N/BRONX//NY/10461
Journal: JOURNAL OF IMMUNOLOGY, 1996, V157, N8 (OCT 15), P3569-3576
ISSN: 0022-1767
Language: ENGLISH Document Type: ARTICLE
Abstract: In this work, we studied the expression of type II nitric oxide synthase (NOS) in primary cultures of human astrocytes and microglia, Cytokine-activated human fetal astrocytes expressed a 4.5-kb type II NOS mRNA that was first evident at 8 h, steadily increased through 48 h, and persisted through 72 h, The inducing signals for astrocyte NOS II mRNA expression were in the order IL-1 beta + IFN-gamma > IL-1 beta
+ TNF-alpha > IL-1 beta, SDS-PAGE analysis of cytokine-stimulated astrocyte cultures revealed an approximately 130-kDa single NOS II band
that was expressed strongly at 48 and 72 h (72 h > 48 h), Specific NOS II immunoreactivity was detected in cytokine-%%%treated%%% astrocytes,
both in the cytosol and in a discrete paranuclear region, which corresponded to Golgi-like membranes on immunoelectron microscopy, In human microglia, cytokines and LPS failed to induce NOS II expression, while the same stimuli readily induced TNF-alpha expression, In cytokine-%%%treated%%% human astrocytes, neither NOS II mRNA/protein
expression nor nitrite production was inhibited by %%%TCF%%%-beta, IL-4, or IL-10, In contrast, IL-1 receptor antagonist exerted near complete inhibition of NOS II mRNA and nitrite induction, Monocyte chemoattractant peptide-1 mRNA was induced in TGF-beta-%%%treated%%%
astrocytes, demonstrating the presence of receptors for TGF-beta in astrocytes. These results confirm that in humans, cytokines stimulate astrocytes, but not microglia, to express NOS II belonging to the high output nitric oxide system similar to that found in rodent macrophages. They also show that the regulation of type II NOS expression in human glia differs significantly from that in rodent glia, A crucial role for the IL-1 pathway in the regulation of human astrocyte NOS II is shown, suggesting a potential role for IL-1 as a regulator of astrocyte activation in vivo.

3/7/4 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04729634 Genuine Article#: UD418 Number of References: 220
Title: MEDIATORS, CYTOKINES, AND GROWTH-FACTORS IN LIVER LUNG INTERACTIONS
Author(s): PANOS RJ; BAKER SK
Corporate Source: NORTHWESTERN UNIV,SCH MED,DEPT MED,DIV PULM,ROOM
777,PASSAVANT PAVILION,303 E SUPER ST/CHICAGO//IL/60611; LAKESIDE VET
ADM MED CTR/CHICAGO//IL/00000
Journal: CLINICS IN CHEST MEDICINE, 1996, V17, N1 (MAR), P151&
ISSN: 0272-5231
Language: ENGLISH Document Type: REVIEW
Abstract: Multiple mediators have been implicated in the interactions between the liver and the lungs in various disease states. The best characterized mediator of liver-lung interaction is alpha(1)-antitrypsin. Several cytokines and mediators may be involved in the pathogenesis of the hepatopulmonary syndrome and in the cytokine cascades that are activated in systemic inflammatory states such as acute respiratory distress syndrome. Hepatocyte growth factor or %%%scatter%%% %%%factor%%% is a recently described peptide with a broad
range of biologic effects that may mediate lung-liver interactions.

3/7/5 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03241474 Genuine Article#: NQ732 Number of References: 49
Title: INCREASED %%%TCF%%%-BETA AND DECREASED ONCOGENE EXPRESSION BY
OMEGA-3-FATTY-ACIDS IN THE SPLEEN DELAYS ONSET OF AUTOIMMUNE-DISEASE IN
B/W MICE
Author(s): FERNANDES G; BYSANI C; VENKATRAMAN JT; TOMAR V; ZHAO WG
Corporate Source: UNIV TEXAS,HLTH SCI CTR,DEPT MED,7703 FLOYD CURL DR/SAN
ANTONIO//TX/78284; UNIV TEXAS,HLTH SCI CTR,DEPT MICROBIOL/SAN
ANTONIO//TX/78284; UNIV TEXAS,HLTH SCI CTR,DEPT PHYSIOL/SAN
ANTONIO//TX/78284
Journal: JOURNAL OF IMMUNOLOGY, 1994, V152, N12 (JUN 15), P5979-5987
ISSN: 0022-1767
Language: ENGLISH Document Type: ARTICLE
Abstract: This study was designed to investigate the mechanisms by which marine lipids rich in long chain omega-3 fatty acids inhibit autoimmune disease and prolong the survival rate in female (NZB/NZW) F1 (B/W) mice, an animal model for human SLE. Nutritionally adequate semipurified diets containing at 10% either corn oil (CO) or fish oil (FO) were fed from 1 mo of age and were monitored for proteinuria and survival. Proteinuria was detected earlier and became progressively severe in CO-fed mice. The average life span was significantly shortened by the CO diet (266.7 days +/- 12.5), whereas FO extended the survival significantly (402.1 days +/- 26.1; p < 0.001). A cross-sectional study at 6.5 mo of age revealed an increased proliferative response to T cell mitogens including bacterial superantigens and decreased serum anti-dsDNA Ab titers in the FO group compared with the CO group. Furthermore, splenocytes from the FO group
when stimulated with Con A had higher IL-2 and lower IL-4 production similar to that of young (3.5 mo) mice. Flow cytometric analyses of splenocytes revealed lower Ig(+), higher lymphocyte endothelial cell adhesion molecule-1, and lower Pgp-1(+) cells within CD4(+) and CD8(+) subsets in FO-fed mice. Also, elevated IL-2 and IL-4 and significantly higher TGF-beta 1 and lower c-myc and c-ras mRNA expression and higher
TGF-beta 1 and significantly lower c-Myc and c-Ha-Ras proteins were detected in spleens of FO-fed mice. Fatty acid analysis revealed significantly higher linoleic (18:2 omega-6) and arachidonic (20:4 omega-6) acid levels in splenocytes of the CO-fed group and higher eicosapentanoic (20:5 omega-3) and docosahexanoic (22:6 omega-3) acid levels in the FO-fed group, indicating that changes in membrane fatty acid composition may contribute to the altered immune function and gene expression during the development of murine SLE.

3/7/6 (Item 1 from file: 73)

DIALOG(R)File 73:EMBASE

10833011 EMBASE No: 2000314204
%%%Modulation%%% of gene expression in critical illness: A new millennium
or a brave new world?
Weiss Y.G.; Deutschamn C.S.
Dr. C.S. Deutschamn, University Pennsylvania, Department of Anesthesia, Philadelphia, PA United States
Critical Care Medicine (CRIT. CARE MED.) (United States) 2000, 28/8 (3078-3079)
CODEN: CCMDC ISSN: 0090-3493
DOCUMENT TYPE: Journal; Editorial
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 23

3/7/7 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07913295 EMBASE No: 1999386716
Cytokines, for better or worse?
Simpson K.J.
Dr. K.J. Simpson, Centre Liver and Digestive Disorders, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW United Kingdom
AUTHOR EMAIL: ksimp@srv1.med.ed.ac.uk
European Journal of Gastroenterology and Hepatology (EUR. J. GASTROENTEROL. HEPATOL.) (United Kingdom) 1999, 11/9 (957-966)
CODEN: EJGHE ISSN: 0954-691X
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 36

Cytokines play an important role in the pathogenesis of many diseases including liver failure. Both newly described and 'classic' pro-inflammatory cytokines, such as tumour necrosis factor-alpha, have been implicated in both hepatic injury and liver regeneration. In addition, increased circulating concentrations of these cytokines suggest they may have a hormone-like endocrine effect on tissues distant to their production, leading to the hypotension, lung injury and cerebral oedema that occur in such patients. Increased understanding of the cytokine networks involved in acute liver failure may lead to the development of novel therapies, which may %%%reduce%%% the requirement for liver transplantation in this condition.

3/7/8 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07817545 EMBASE No: 1999289951
Effects of deletion-type human hepatocyte growth factor on murine septic model
Kondo H.; Tani T.; Kodama M.
Dr. H. Kondo, First Department of Surgery, Shiga University of Medical Science, Shiga 520-2192 Japan
Journal of Surgical Research (J. SURG. RES.) (United States) 1999, 85/1 (88-95)
CODEN: JSGRA ISSN: 0022-4804
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 29

Background. %%%Sepsis%%% is known to be the main cause of multiple organ
failure. The liver especially is vulnerable to the stress of infection. In this study, the effects of deletion-type human hepatocyte growth factor (dHGF) on a murine septic model were studied. Materials and methods. %%%Sepsis%%% was induced in male adult Sprague-Dawley rats by cecal ligation and puncture method (CLP). Controls were given a sham operation. Intravenous injection of 1000 mug/kg dHGF or the same volume of vehicle was
given every 12 h for 3 days before and/or after the CLP from a central vein catheter inserted 1 week prior to the operation. The daily percentage of survival after CLP was followed up for 1 week, and blood samples and liver specimens were collected from the surviving animals 72 h after CLP or sham operation. Results. The survival rate, the degree of liver damage and liver protein synthesis, and coagulation function were all favorable in the dHGF-%%%treated%%% animals compared to the untreated animals. Immunohistochemical staining showed that dHGF %%%prevented%%% the disappearance of thrombomodulin (TM) in liver sinusoid endothelium. Conclusions. dHGF appears to %%%prevent%%% liver injury caused by disturbance of microcirculation through preservation of TM expression and the antithrombotic function in the endothelium of sinusoids. dHGF also facilitates repair of damaged hepatic tissue by stimulating regeneration of the cells and by preserving hepatic functions such as protein synthesis. dHGF exerts protective effects on even quiescent hepatocytes, but is most effective on injured but competent hepatocytes.

3/7/9 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

07744750 EMBASE No: 1999227000
Hepatocyte growth factor %%%prevents%%% endotoxin-induced lethal hepatic
failure in mice
Kosai K.-I.; Matsumoto K.; Funakoshi H.; Nakamura T.
Dr. T. Nakamura, Department of Oncology, Biomedical Research Center, Osaka University Medical School, Suita, Osaka 565-0871 Japan
AUTHOR EMAIL: nakamura@onbich.med.osaka-u.ac.jp
Hepatology (HEPATOLOGY) (United States) 1999, 30/1 (151-159)
CODEN: HPTLD ISSN: 0270-9139
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 54

%%%Sepsis%%% and endotoxemia are involved in the development of fulminant
hepatic failure, the prognosis of which is extremely poor and the mortality is high, with no available effective therapy. Here, we report that hepatocyte growth factor (HGF) exerts potent antiapoptotic effects in vivo and effectively %%%prevents%%% endotoxin-induced fulminant hepatic failure
in mice. The animals were intraperitoneally injected three times with 120 mug human recombinant HGF or saline 6 hours and 30 minutes before and 3 hours after an intraperitoneal injection of lipopolysaccharide (LPS) and D-galactosamine (GAlN). Administration of LPS + GalN, without HGF, rapidly led to massive hepatocyte apoptosis and severe liver injury, and all mice died of hepatic failure within 8 hours. In contrast, administration of human recombinant HGF strongly suppressed extensive progress of hepatocyte
apoptosis and the liver injury induced by LPS + GAlN, and 75% of the HGF-%%%treated%%% mice survived. Moreover, HGF strongly induced Bcl-xL expression and blocked apoptotic signal transduction upstream of CPP32 (caspase-3) in the liver, thereby leading to inhibition of massive hepatocyte apoptosis. We suggest that HGF may well have the potential to %%%prevent%%% fulminant hepatic failure, at least through its potent antiapoptotic action.

3/7/10 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

07098877 EMBASE No: 1997380741
Cytokines and the liver
Simpson K.J.; Lukacs N.W.; Colletti L.; Strieter R.M.; Kunkel S.L.
K.J. Simpson, Ctr. for Liver/Digestive Disorders, Royal Infirmary, Edinburgh EH3 9YW United Kingdom
AUTHOR EMAIL: ksimp@srV2.med.ed.ac.uk
Journal of Hepatology (J. HEPATOL.) (Denmark) 1997, 27/6 (1120-1132)
CODEN: JOHEE ISSN: 0168-8278
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 131

3/7/11 (Item 6 from file: 73)

DIALOG(R)File 73:EMBASE

06633807 EMBASE No: 1996298618
Effects of hepatocellular mitogens on cytokine-induced nitric oxide synthesis in human hepatocytes
Liu Z.-Z.; Cui S.; Billiar T.R.; Dorko K.; Halfter W.; Geller D.A.; Michalopoulos G.; Beger H.-G.; Albina J.; Nussler A.K.
Department General Surgery, University of Ulm, Park Street,D-89073 Ulm

Germany
Journal of Leukocyte Biology (J. LEUKOCYTE BIOL.) (United States) 1996
, 60/3 (382-388)
CODEN: JLBIE ISSN: 0741-5400
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The synthesis of induced nitric oxide (NO) is regulated by several cytokines, including growth factors produced following hepatic injury and inflammation. However, little information is available on the role of growth factors in regulating the inducible NO synthase in human hepatocytes. The capacity of hepatocellular mitogens (HGF, EGF, and TGF-alpha) to regulate the inducible NO synthase (iNOS) was studied in human hepatocytes incubated with inflammatory cytokines and lipopolysaccharide (LPS). Furthermore, the effects of hepatic mitogens on NO-induced changes in DNA and protein synthesis was studied. It was found that NO-mediated decrease of protein and DNA synthesis were partially reversed by the mitogens. This was associated with a downregulation in cytokine-mediated hepatocyte NO formation, iNOS mRNA expression, and NOS
enzyme activity. Cytokine-induced NO formation or SNAP, an NO donor, added
with cytokines increased hepatocyte chromatin condensation but no DNA fragmentation was observed. The increase in chromatin condensation was partially reversed by hepatic mitogens and corresponded with the inhibition of NO production. Thus, the hepatic mitogens, HGF, EGF, and TGF-alpha, all suppress iNOS expression and it is the suppression of iNOS that appears to be responsible for the mitogen-%%%reduced%%% preservation of DNA and protein synthesis and %%%prevention%%% of chromatin condensation.

3/7/12 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

06345921 EMBASE No: 1996002326
Significant elevation of serum human hepatocyte growth factor levels in patients with acute pancreatitis
Ueda T.; Takeyama Y.; Toyokawa A.; Kishida S.; Yamamoto M.; Saitoh Y.
First Department of Surgery, Kobe University School of Medicine, 7-5-2 Kusunoki-cho,Chuo-ku, Kobe 650 Japan
Pancreas (PANCREAS) (United States) 1996, 12/1 (76-83)
CODEN: PANCE ISSN: 0885-3177
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Serum levels of human hepatocyte growth factor (HGF) were determined in 38 patients with acute pancreatitis by an enzyme-linked immunosorbent assay. The mean value of serum HGF levels on admission in the 38 patients was 1.69 +/- 0.40 (SEM) ng/ml. In 35 patients, serum HGF levels were found to be positive (>0.39 ng/ml), with an incidence of 92.1%. In 17 patients, they were >1.0 ng/ml, which was the cutoff value for fulminant hepatic failure. Serum HGF levels in the patients with severe acute pancreatitis (2.30 +/- 0.61 ng/ml; mean +/- SEM) were significantly higher than those in the patients with mild and moderate acute pancreatitis (0.63 +/- 0.06 ng/ml). Sixteen of seventeen patients whose serum HGF levels were >1.0 ng/ml were evaluated as severe acute pancreatitis. Serum HGF levels were significantly elevated in the patients with higher Ranson scores, higher APACHE II scores, or higher computed tomography grades. Serum HGF levels in
the patients with organ dysfunction (liver, kidney, or lung) were significantly higher than those in the patients without organ dysfunction. Moreover, serum HGF levels on admission in the nonsurvivors (3.17 +/- 1.30 ng/ml) were significantly higher than those in the survivors (1.22 +/- 0.33 ng/ml). The mortality rate of the patients showing serum HGF levels >2.0 ng/ml on admission was 50%. In the patients with a lethal outcome, the mean serum HGF level remained constantly >2.50 ng/ml during hospitalization. The serum HGF level reflected the clinical course of the disease rapidly and distinctly. Serum HGF levels increased with complications such as organ failure, infected pancreatic necrosis, and %%%sepsis%%% and decreased with
successful intensive and surgical %%%treatments%%%. These results suggest
that serum human HGF levels may reflect the severity, organ dysfunction, and prognosis in acute pancreatitis.

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OR REDUC?
          OR AMELORIAT?)
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    3154219  TUMOR
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7/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13595299 BIOSIS NO.: 200200224120
HIV-associated nephropathy (HIVAN) is associated with altered expression of
%%%scatter%%% %%%factor%%% (SF) and tissue metalloprotease inhibitor
protein (TIMP)-4.
AUTHOR: Franki Nicholas(a); Celiker Mahmut Y(a); Shi Eric(a); Fan Saijun(a)
; Kapasi Aditi A(a); Singhal Pravin C(a)
AUTHOR ADDRESS: (a)Medicine, LIJ Medical Center, New Hyde Park, NY**USA
JOURNAL: Journal of the American Society of Nephrology 11 (Program and Abstract Issue):p84A September, 2000
MEDIUM: print
CONFERENCE/MEETING: 33rd Annual Meeting of the American Society of Nephrology and the 2000 Renal Week Toronto, Ontario, Canada October 10-16, 2000
ISSN: 1046-6673
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Matrix remodeling has been considered to be the determinant for
the progression of interstitial fibrosis in HIVAN. TIMP-4 not only participates in matrix remodeling, but has also been reported to alter cell growth; whereas SF is known to play a role in tissue repair and morphogenesis in a variety of tissues and cells. We studied the tubular cell expression of SF and TIMP-4 in renal biopsy tissue (5 in each group) of renal cancer patients (noncancerous tissue), HIVAN, and idiopathic focal glomerulosclerosis. Formalin fixed and paraffin embedded tissue sections were stained with hematoxylin and eosin and examined under light microscope. To determine the expression of TIMP-4 and SF, immunohistochemical studies were carried out using anti-TIMP-4 and anti-SF antibodies. Tubular cell staining of TIMP-4 and SF was graded from 0 to 3+. Patients with renal cancer (considered as controls) showed normal glomeruli and tubules in noninvolved areas. Except loci of tubular atrophy and mononuclear cell infiltration, renal interstitium was well preserved in FGS specimens. However, patients with HIVAN showed extensive
structural changes in the interstitium in the form of microcystic dilatation of tubules, tubular cell proliferation and degeneration. Immunohistochemical studies revealed positive staining for SF in 71% and 25% of the tubules in HIVAN and FGS specimens respectively. However, normal kidney tissue from cancer patients showed no staining for SF. As for TIMP-4, all specimens from cancer patients showed positive staining (1+ to 3+). On the other hand, only 60% of specimens showed positive staining (1+) for TIMP-4 in HIVAN as well as in FGS. These results suggest that SF may be playing a role in tubular cell regeneration in HIVAN. In addition, altered expression of TIMP-4 in HIVAN and FGS may be
contributing to matrix remodeling.

7/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13359710 BIOSIS NO.: 200100566859
Phosphorylation of tyrosine 972 of the Helicobacter pylori CagA protein is essential for induction of a scattering phenotype in gastric epithelial cells.
AUTHOR: Backert Steffen; Moese Stefan; Selbach Matthias; Brinkmann Volker;
Meyer Thomas F(a)
AUTHOR ADDRESS: (a)Abt. Molekulare Biologie, Max-Planck-Institut fuer Infektionsbiologie, Schumannstr. 20/21, D-10117, Berlin:
meyer@mpiib-berlin.mpg.de**Germany
JOURNAL: Molecular Microbiology 42 (3):p631-644 November, 2001
MEDIUM: print
ISSN: 0950-382X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Helicobacter pylori colonizes the human stomach and is the causative agent of a variety of gastric diseases. After %%%bacterial%%% attachment, the H. pylori CagA protein is translocated into gastric epithelial cells and tyrosine phosphorylated. This process is associated with characteristic cytoskeletal rearrangements, resulting in a %%%scatter%%% %%%factor%%%-like ('hummingbird') phenotype. In this study,
using a cagA mutant complemented with wild-type cagA and transiently expressing CagA in AGS cells, we have demonstrated that translocated CagA
is necessary for rearrangements of the actin cytoskeleton to occur. Anti-phosphotyrosine immunoblotting studies and treatment of %%%infected%%% cells with phosphotyrosine kinase inhibitors suggested that not only translocation but also phosphorylation of CagA is important in this process. Transient expression of CagA-green fluorescent protein (GFP) fusion proteins and two-dimensional gel electrophoresis of CagA protein species demonstrated tyrosine phosphorylation in the C-terminus. Site-directed mutagenesis of CagA revealed that tyrosine residue 972 is essential for induction of the cellular phenotype. We have also demonstrated that translocation and phosphorylation of CagA is necessary but not sufficient for induction of the hummingbird phenotype in AGS cells, indicating the involvement of as yet unidentified %%%bacterial%%% factor(s).

7/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13137705 BIOSIS NO.: 200100344854
Induction of c-Met proto-oncogene by Epstein-Barr virus latent membrane protein-1 and the correlation with cervical lymph node metastasis of nasopharyngeal carcinoma.
AUTHOR: Horikawa Toshiyuki; Sheen Tzung-Shiahn; Takeshita Hajime; Sato Hiroshi; Furukawa Mitsuru; Yoshizaki Tomokazu(a)
AUTHOR ADDRESS: (a)Department of Otolaryngology, School of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa, 920-8641:
tomoy@orl.m.kanazawa-u.ac.jp**Japan
JOURNAL: American Journal of Pathology 159 (1):p27-33 July, 2001
MEDIUM: print
ISSN: 0002-9440
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Nasopharyngeal carcinoma (NPC) is distinctive in head and neck carcinomas for its close association with Epstein-Barr virus and its highly metastatic nature. Up-regulation of cell motility is essential for enhancement of metastatic potential. The expression of c-Met proto-oncogene, a high-affinity receptor for hepatocyte growth factor/ %%%scatter%%% %%%factor%%%, has been reported to correlate with metastatic ability of the tumor cell. We observed close association of c-Met expression with cervical lymph node metastasis (P=0.0272) in 39 NPC
specimens studied immunohistochemically. Epstein-Barr virus-encoding latent membrane protein-1 (LMP-1) is a primary oncogene and is suggested to enhance the metastatic property of NPC. Previously, we reported that LMP-1 enhanced the motility of Madin-Darby canine kidney (MDCK) epithelial cells that was mediated by activation of Ets-1 transcription factor. Therefore, we examined the interrelationships of LMP-1, Ets-1, and c-Met. In immunohistochemical studies, the expression of LMP-1, Ets-1, and c-Met correlated significantly with each other in NPC (LMP-1 versus Ets-1, P<0.0001; Ets-1 versus c-Met, P=0.0012; LMP-1 versus Met, P=0.0005). Transfection of LMP-1-expressing plasmid in MDCK cells

induced
c-Met protein expression. The c-Met protein was also induced by Ets-1 expression, and induction of c-Met by LMP-1 was suppressed by introducing a dominant-negative form of Ets-1 in LMP-1-expressing MDCK cells. These results suggest that LMP-1 induces c-Met through the activation of Ets-1, which may contribute in part to the highly metastatic potential of NPC.

7/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12562525 BIOSIS NO.: 200000316027
Induction of HHV-8 lytic cycle replication by inflammatory cytokines produced by HIV-1-%%%infected%%% T cells.
AUTHOR: Mercader Mari; Taddeo Brunell; Panella Jeffery R; Chandran Bal; Nickoloff Brian J; Foreman Kimberly E
AUTHOR ADDRESS: (a)Department of Pathology, Skin Cancer Research Laboratories, Loyola University Oncology Institute, 2160 South First Avenue, Room 302, Maywood, IL, 60153-5385**USA
JOURNAL: American Journal of Pathology 156 (6):p1961-1971 June, 2000
MEDIUM: print
ISSN: 0002-9440
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Human herpesvirus 8 (HHV-8) is a gamma2-herpesvirus consistently
identified in Kaposi's sarcoma (KS), primary effusion lymphoma, and multicentric Castleman's disease. Although HHV-8 %%%infection%%% appears
to be necessary, it may not be sufficient for development of KS without the involvement of other cofactors. One potentially important cofactor is HIV-1. HIV-1-%%%infected%%% cells produce HIV-1-related proteins and cytokines, both of which have been shown to promote growth of KS cells in vitro. Though HIV-1 is not absolutely necessary for KS development, KS is the most frequent neoplasm in AIDS patients, and AIDS-KS is recognized as
a particularly aggressive form of the disease. To determine whether HIV-1 could participate in the pathogenesis of KS by modulating HHV-8 replication (rather than by inducing immunodeficiency), HIV-1-%%%infected%%% T cells were cocultured with the
HHV-8-%%%infected%%% cell
line, BCBL-1. The results demonstrate soluble factors produced by or in response to HIV-1-%%%infected%%% T cells induced HHV-8 replication, as
determined by production of lytic phase mRNA transcripts, viral proteins, and detection of progeny virions. By focusing on cytokines produced in the coculture system, several cytokines known to be important in growth and proliferation of KS cells in vitro, particularly Oncostatin M, hepatocyte growth factor/%%%scatter%%% %%%factor%%%, and interferon-gamma, were found to induce HHV-8 lytic replication when added
individually to BCBL-1 cells. These results suggest specific cytokines can play an important role in the initiation and progression of KS through reactivation of HHV-8. Thus, HIV-1 may participate more directly than previously recognized in KS by promoting HHV-8 replication and, hence, increasing local HHV-8 viral load.

7/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12439849 BIOSIS NO.: 200000193351
Enhancement of hepatocyte growth factor (%%%scatter%%% %%%factor%%%)
production by human gingival fibroblasts in culture stimulated with Porphyromonas gingivalis fimbriae.
AUTHOR: Sugiyama A; Ogawa T; Daikuhara Y; Takada H(a)
AUTHOR ADDRESS: (a)Department of Microbiology and Immunology, Tohoku
University School of Dentistry, Sendai, 980-8575**Japan
JOURNAL: Journal of Medical Microbiology 49 (4):p319-325 April, 2000
ISSN: 0022-2615
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Hepatocyte growth factor (HGF), also known as %%%scatter%%%
%%%factor%%% (SF), is a motogen, mitogen and morphogen produced by mesenchymal cells that mainly acts on epithelial cells and is involved in osteoclast stimulation. This study examined the possible enhanced production of HGF/SF by human gingival fibroblasts upon stimulation with killed cells of Porphyromonas gingivalis strain 381 and its representative bioactive cellular components, fimbriae and lipopolysaccharide (LPS). P. gingivalis whole cells enhanced the production of HGF/SF detected by ELISA in culture supernates of the fibroblasts. Fimbriae prepared from P. gingivalis exhibited powerful HGF/SF-inducing activity in a concentration-dependent manner, with peak activity observed at 100-200 mug/ml. The fimbriae-induced HGF/SF mRNA
expression by the cells was also detected by reverse transcription-PCR. P. gingivalis LPS exhibited weak HGF/SF-inducing activity. The study also examined the HGF/SF-inducing activity of seven synthetic peptides corresponding to the segments of P. gingivalis fimbrial subunit protein. The peptides of residues 282-301 and 302-321, which exhibited antagonistic effects against P. gingivalis fimbriae-binding to human gingival fibroblasts in a previous study, showed weak activity, whereas other non-antagonistic peptides showed no significant activity. These findings indicated that P. gingivalis fimbriae enhanced production of HGF/SF by human gingival fibroblasts, whereas synthetic peptide segments of fimbrial subunit protein were not sufficient to exert the activity.
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        OR AMELORIAT?)
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8/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12071214 BIOSIS NO.: 199900366063
Differential expression of c-Met in Kaposi's sarcoma according to progression stage and HIV %%%infection%%% status.
AUTHOR: Puig Lluis(a); Fernandez-Figueras Maria-Teresa; Penin Rosa-Maria;

4. d

Esquius Mireia; Alomar Agustin; Ariza Aurelio
AUTHOR ADDRESS: (a)Department of Dermatology, Hospital de la Santa Creu i
Sant Pau, Sant Antoni Maria Claret 167, 0**Spain
JOURNAL: Journal of Cutaneous Pathology 26 (5):p227 - 231 May, %%%1999%%%
ISSN: 0303-6987
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Several cytokines, growth factors and the HIV transactivator Tat
have been shown to be involved in the pathogenesis of Kaposi's sarcoma (KS). Hepatocyte growth factor/%%%scatter%%% %%%factor%%% (HGF) is an
angiogenic cytokine that stimulates proliferation of spindle cells cultured from human KS lesions. The receptor for HGF, the c-Met protein, is expressed by endothelial cells, dermal dendrocytes and KS tumor cells both in vitro and in vivo. KS cells synthesize and secrete HGF and express the hepatocyte growth factor receptor (c-Met), thus providing an autocrine loop for tumor proliferation and neovascularization which can be enhanced by proinflammatory cytokines. We studied the immunohistochemical expression of c-Met in 40 cases of classical Kaposi's sarcoma (C-KS) and AIDS-associated cutaneous Kaposi's sarcoma (AIDS-KS),
including 22 plaque stage lesions (12 AIDS-KS cases) and 18 tumor stage lesions (7 AIDS-KS cases). Statistically significant differences in the average intensity of immunohistochemical staining according to the type of lesions (progression stages) and the serologic status of the patients were identified. The staining intensity of c-Met was stronger in tumors than in plaques. When only plaques were taken into consideration, the mean staining score was nearly twice as high in C-KS as in AIDS-KS.

8/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11844197 BIOSIS NO.: 199900090306
Somatic mutations in the kinase domain of the Met/hepatocyte growth factor
receptor gene in childhood hepatocellular carcinomas.
AUTHOR: Park Won Sang; Dong Seung Myung; Kim Su Young; Na Eun Young; Shin
Min Sun; Pi Jae Ho; Kim Bum Jun; Bae Jeong Hoon; Hong Young Ki; Lee Kyo Sun; Lee Sug Hyung; Yoo Nam Jin; Jang Ja June; Pack Svetlana; Zhuang Zhengping; Schmidt Laura; Zbar Berton; Lee Jung Young(a)
AUTHOR ADDRESS: (a)Dep. Pathol., Catholic Univ. Med. Coll., Seoul 137-701**
South Korea
JOURNAL: Cancer Research 59 (2):p307-310 Jan. 15, %%%1999%%%
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The MET protooncogene encodes a transmembrane tyrosine kinase
identified as the receptor of a polypeptide known as hepatocyte growth factor/%%%scatter%%% %%%factor%%%. We performed PCR-based single-strand
conformational polymorphism and sequencing analysis of the tyrosine kinase domain of the MET gene (exon 15-19) in 75 primary liver cancers. Three missense mutations were detected exclusively in 10 childhood hepatocellular carcinomas (HCCs), while no mutations were detected in 16 adult HCCs, 21 cholangiocarcinomas, or 28 hepatoblastomas. The extremely
short incubation period from hepatitis B virus %%%infection%%% to the genesis of childhood HCC as compared with the adult HCC suggests that there may be an additional mechanism that accelerates the carcinogenesis of childhood HCC. Our results indicate that mutations of the tyrosine kinase domain of the MET gene may be involved in the acceleration of the carcinogenesis in childhood HCC.

8/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11744570 BIOSIS NO.: 199800525266
Effect of HGF (%%%scatter%%% %%%factors%%%) in the regulation of molecules
involved in angiogenesis (VE-cadherin, alphavbeta3, and VEGF) during chronic viral hepatitis.
AUTHOR: Garcia-Monzon C; Zubia-Lauzurica I; Majano P L; Moreno-Otero R
AUTHOR ADDRESS: Liver Unit, Hosp. Univ. Princesa, Madrid**Spain
JOURNAL: Hepatology 28 (4 PART 2):p240A Oct., %%%1998%%%
CONFERENCE/MEETING: Biennial Scientific Meeting of the International Association for the Study of the Liver and the 49th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Chicago, Illinois, USA November 4-10, 1998
SPONSOR: International Association for the Study of the Liver
ISSN: 0270-9139
RECORD TYPE: Citation
LANGUAGE: English

8/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

11544335 BIOSIS NO.: 199800325667
Mechanisms of sperm deficiency in male accessory gland %%%infection%%%.
AUTHOR: Depuydt C; Zalata A; Christophe A; Mahmoud A; Comhaire F(a)
AUTHOR ADDRESS: (a)Univ. Hosp., De Pintelaan 185, 9000 Ghent**Belgium
JOURNAL: Andrologia 30 (SUPPL. 1):p29-33 %%%1998%%%
ISSN: 0303-4569
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The presence of 2 million or more peroxidase-positive white blood
cells per ml of semen, or the diagnosis of male accessory gland %%%infection%%%, is associated with important biochemical and biological changes in semen plasma and in the spermatozoa, reducing their fertilizing potential in vitro and in vivo (e.g., during intrauterine insemination). In addition to the effects of reactive oxygen species, and its influence on the essential fatty acid composition of the sperm membrane, potentially unfavourable effects can occur through the intermediate of increased concentrations of certain cytokines, and decreased activity of enzymes such as alpha-glucosidase. In contrast, lower numbers of white blood cells may exert beneficial effects on spermatozoa thanks to the increased production of hepatocyte growth factor/%%%scatter%%% %%%factor%%% (a tissue repairing substance), and the
stimulation of immuno-competent cells by particular cytokines (e.g., Interleukin-6).

8/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11195348 BIOSIS NO.: 199799816493
Epithelial-stromal interactions modulating penetration of matrigel
membranes by HPV 16-immortalized keratinocytes.
AUTHOR: Turner Mary A; Darragh Teresa; Palefsky Joel M(a)
AUTHOR ADDRESS: (a)Dep. Lab. Med., Box 0100, Univ. California, San
Francisco, CA 94143**USA
JOURNAL: Journal of Investigative Dermatology 109 (5):p619-625 %%%1997%%%
ISSN: 0022-202X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The role of epithelial-stromal interactions in the progression of human papillomavirus-associated squamous intraepithelial lesions to invasive cervical cancer is poorly understood. Using the Matrigel artificial basement membrane assay as a model of keratinocyte invasion, the effects of selected growth factors on penetration of human

papillomavirus 16-immortalized keratinocytes through Matrigel were studied. Also studied in this model were the effects of conditioned media from fibroblast lines derived from normal cervical tissues (normal fibroblasts) and adjacent cervical cancer biopsies (tumor-associated fibroblasts) and from primary keratinocytes. Addition of basic fibroblast growth factor, transforming growth factor-alpha, and hepatocyte growth factor/%%%scatter%%% %%%factor%%% or conditioned media from tumor-associated fibroblasts to the Matrigel resulted in near-doubling of penetration of human papillomavirus 16-immortalized keratinocytes, whereas transforming growth factor-beta, platelet derived growth factor-B, or conditioned media from primary keratinocytes decreased penetration 10-fold. Antibodies to basic fibroblast growth factor abrogated the stimulatory effects of conditioned media from tumor-associated fibroblasts on keratinocyte penetration, whereas antibodies to transforming growth factor-beta abrogated the inhibitory effects of conditioned media from normal fibroblasts on keratinocyte penetration. S1 nuclease protection and enzyme-linked immunosorbent assay
showed increased expression of transforming growth factor-beta and decreased expression of basic fibroblast growth factor in normal compared with tumor-associated fibroblasts. Messenger RNA in situ hybridization of five cervical cancer biopsies demonstrated basic fibroblast growth factor expression in stromal cells surrounding nests of invading keratinocytes. Epithelial-stromal interactions mediated by growth factors such as transforming growth factor-beta and basic fibroblast growth factor modulate penetration of human papillomavirus 16-immortalized keratinocytes through Matrigel in vitro and these interactions may also be operative in vivo.

8/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11001005 BIOSIS NO.: 199799622150
Glycoconjugate cross-talk in metastatic cancer cells, leucocytes, parasites and %%%bacteria%%%.
AUTHOR: Leroy A; Noet V; Mareel M(a); Nelis H
AUTHOR ADDRESS: (a)Lab. Exp. Cancerol., University Hosp., De Pintelaan 185,
B-9000 Gent**Belgium
JOURNAL: Biochemical Society Transactions 25 (1):p228-234 %%%1997%%%
CONFERENCE/MEETING: 659th Meeting of the Biochemical Society London,
England, UK September 4-6, 1996
ISSN: 0300-5127
RECORD TYPE: Citation
LANGUAGE: English

8/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10784126 BIOSIS NO.: 199799405271
Hepatocyte growth factor/%%%scatter%%% %%%factor%%% promotes adhesion of
lymphoma cells to extracellular matrix molecules via alpha-4-beta-1 and alpha-5-beta-1 integrins.
AUTHOR: Weimar Iris S; De Jong Daphne; Muller Egbert J; Nakamura Toshikazu;
Van Gorp Joost M H H; De Gast Gijsbert C; Gerritsen Winald R(a)
AUTHOR ADDRESS: (a)Dep. Immunol./Med. Oncol., Netherlands Cancer Inst.,
Plesmanlaan 121, 1066 CX Amsterdam**Netherlands
JOURNAL: Blood 89 (3):p990-1000 %%%1997%%%
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Hepatocyte growth factor (HGF)/%%%scatter%%% %%%factor%%% (SF) is
the ligand for a tyrosine kinase cell surface receptor encoded by the MET protooncogene (c-MET). HGF/SF can induce proliferation and motility in epithelial cells and promotes invasion of carcinoma cells and NIH3T3 fibroblasts transfected with both HGF/SF and c-MET genes. Our results show that HGF/ SF and c-MET also play a role in adhesion and invasion of human lymphoma cells. c-MET mRNA is expressed in hemopoietic cells, such as hemopoietic progenitor cells (CD34+ cells) in bone marrow (BM) and mobilized peripheral blood, immature B cells in cord blood and BM, and germinal center B-centroblasts. In normal peripheral blood B cells, which are c-MET-, c-MET expression was induced by PMA, ConA, HGF/ SF, and Epstein-Barr virus (EBV) %%%infection%%%. Using immunohistochemistry, we
detected c-MET on the cell surface of large activated centroblasts in lymph nodes from patients with B-non-Hodgkin's lymphoma and Hodgkin's disease. In the latter group, c-MET expression correlated well with the presence of EBV. Because HGF/SF and c-MET promote metastasis of carcinoma
cells, we studied the effects of c-MET stimulation by HGF/SF of B-lymphoma cells on properties relevant for metastasis, ie, adhesion, migration, and invasion. HGF/SF stimulated adhesion of the c-MET+ B-cell lines to the extracellular matrix molecules fibronectin (FN) and collagen (CN) in a dose dependent manner. However, adhesion to laminin was not affected by HGF/SF. Adhesion to FN was mediated by beta-1-integrins alpha-4-beta-1 (VLA4) and alpha-5-beta-1 (VLA5) since blocking antibodies against beta-1- (CD29), alpha-4(CD49d), or alpha-5- (CD49e) integrin subunits, completely reversed the effect of HGF/SF. Furthermore, HGF/SF
induced adhesion was abrogated by addition of genistein, which blocks protein tyrosine kinases, including c-MET. Addition of HGF/SF resulted in a sixfold increase in migration of cMET B-lymphoma cells through Matrigel, compared to medium alone. In rat fibroblast cultures, HGF/SF doubled the number of c-MET+ B-lymphoma cells that invaded the fibroblast
monolayer. In these adhesion, migration and invasion assays HGF/SF had no effect on c-MET- cell lines. In conclusion, c-MET is expressed or can be induced on immature, activated, and certain malignant B cells. HGF/SF increased adhesion of c-MET+ B-lymphoma cells to FN and CN, mediated via
beta-1-integrins alpha-4-beta-1 and alpha-5-beta-1, and furthermore promoted migration and invasion.

8/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10391855 BIOSIS NO.: 199699013000
Kaposi's sarcoma: Advances and perspectives.
AUTHOR: Schwartz Robert A
AUTHOR ADDRESS: Dermatol., New Jersey Med. Sch., 185 S. Orange Ave.,
Newark, NJ 07103-2714**USA
JOURNAL: Journal of the American Academy of Dermatology 34 (5 PART 1):p
804-814 %%%1996%%%
ISSN: 0190-9622
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Kaposi's sarcoma (KS) is an unusual neoplasm that has proved to be an enigma in many ways since its original description by Kaposi in 1872. Its epidemiology has stimulated tremendous interest, amplified markedly in 1981 when it became known as an original defining part of the complex of immune disorders now known as AIDS. The cell of origin, etiology, and therapy for both AIDS-associated and AIDS-unassociated KS
continue as matters of intense investigation. In fact, whether it is a reactive hyperplasia or a true malignancy is still a matter of debate, as is the concept of multicentricity versus metastases. Epidemiologic studies suggest that a separate agent apart from HIV-1 may cause KS. A newly postulated KS-associated herpes virus may be linked. The role of the HIV-1 tat gene product, basic fibroblast growth factor, %%%scatter%%%
%%%factor%%%, oncostatin M, and other factors that regulate the growth of
KS cells are discussed, as well as therapeutic options.

8/7/9 (Item 9 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

10322626 BIOSIS NO.: 199698777544
Lipoteichoic acid and interleukin 1 stimulate synergistically production of hepatocyte growth factor (%%%scatter%%% %%%factor%%%) in human gingival fibroblasts in culture.
AUTHOR: Sugiyama Akiko; Arakaki Rieko; Ohnishi Tomokazu; Arakaki Naokatu; Daikuhara Yasushi; Takada Haruhiko(a)
AUTHOR ADDRESS: (a)Dep. Microbiol. Immunol., Kagoshima Univ. Dental Sch., 8-35-1 Sakuragaoka, Kagoshima 890**Japan
JOURNAL: Infection and Immunity 64 (4):p1426-1431 %%%1996%%%
ISSN: 0019-9567
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Lipoteichoic acids (LTA) from various gram-positive %%%bacteria%%%, including oral streptococci such as Streptococcus sanguis, enhanced the production of hepatocyte growth factor (HGF) (%%%scatter%%% %%%factor%%%) by human gingival fibroblasts in culture, whereas lipopolysaccharides (LPS) from various gram-negative %%%bacteria%%% did not. In contrast, LPS induced interleukin 1 activity in human gingival epithelial cells in culture, while LTA had little effect. LTA and recombinant human interleukin lot enhanced synergistically the production of HGF/SF in human gingival fibroblast cultures. Recombinant human HGF, in turn, enhanced the proliferation of human gingival epithelial cells in culture.

8/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10178756 BIOSIS NO.: 199698633674
1995 Central Regional Meeting of the Society for Investigative Dermatology.
AUTHOR: Society For Investigative Dermatology
JOURNAL: Journal of Investigative Dermatology 105 (6):p870-872 %%%1995%%%
ISSN: 0022-202X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This meeting contains abstracts of 16 papers covering the immunology, physiology, pathology, biochemistry and treatment of skin of humans, animals and of skin cells in tissue culture.

8/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10146364 BIOSIS NO.: 199698601282
Elevated serum hepatocyte growth factor/%%%scatter%%% %%%factor%%% levels in inflammatory lung disease.
AUTHOR: Maeda Juichiro; Ueki Noboru(a); Hada Toshikazu; Higashino Kazuya
AUTHOR ADDRESS: (a)Third Dep. Intern. Med., Hyogo Coll. Med., 1-1 Mukogawa-che, Nishinomiya, Hyogo 663**Japan
JOURNAL: American Journal of Respiratory and Critical Care Medicine 152 (5 PART 1):p1587-1591 %%%1995%%%
ISSN: 1073-449X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Hepatocyte growth factor/%%%scatter%%% %%%factor%%% (HGF/SF) . plays an important role in tissue repair in liver and renal damage. The clinical significance of this growth factor in these diseases has also been reported. The lung is one of the major sources of HGF/SF; because of this, we investigated serum HGF/SF levels in 26 patients with inflammatory lung disease (15 with interstitial pneumonitis (IP), 11 with %%%bacterial%%% pneumonia (BP)) by enzyme-linked immunosorbent assay. As controls, we measured HGF/SF in the serum of 13 stable outpatients with chronic respiratory failure. All patients had no significant liver or renal dysfunction. Serum HGF/SF levels were significantly elevated in patients with IP (1.16 +- 0.22 ng/ml) or BP (0.96 +- 0.27 ng/ml) compared with those in the control subjects (0.29 +- 0.03 ng/ml, both p lt 0.01). Serum HGF/SF levels in 14 healthy subjects were also studied, and the results (0.30 +- 0.02 ng/ml) were not remarkably different from those of the control subjects. There were no significant correlations between serum HGF/SF levels and C-reactive protein and lactate dehydrogenase. Serum HGF/SF levels in the surviving patients rapidly decreased with treatment, but they did not change in the patients who ultimately died. Our results demonstrate the clinical significance of serum HGF/SF level as a useful indicator of prognosis in inflammatory lung disease.

8/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10032277 BIOSIS NO.: 199598487195
Gene expression in end-stage liver diseases.
AUTHOR: Petrovic L M(a); Ljubimova J Y; Geller S A; Demetriou A A
AUTHOR ADDRESS: (a)Dep. Pathol., Los Angeles, CA**USA
JOURNAL: Journal of Hepatology 23 (SUPPL. 1):p235 %%%1995%%%
CONFERENCE/MEETING: 30th Annual Meeting of the European Association for the Study of the Liver Copenhagen, Denmark August 20-23, 1995
ISSN: 0168-8278
RECORD TYPE: Citation
LANGUAGE: English

8/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10024429 BIOSIS NO.: 199598479347
Biology of hepatocellular carcinoma.
BOOK TITLE: Gastrointestinal cancers: Biology, diagnosis, and therapy
AUTHOR: Ozturk Mehmet
BOOK AUTHOR/EDITOR: Rustgi A K: Ed
AUTHOR ADDRESS: Lab. Mol. Oncol., INSERM CJF 9302, Lyon 69008**France
p511-525 %%%1995%%%
BOOK PUBLISHER: Lippincott-Raven Publishers, 227 East Washington Square, Philadelphia, Pennsylvania 19106, USA
ISBN: 0-7817-0276-3
DOCUMENT TYPE: Book
RECORD TYPE: Citation
LANGUAGE: English

8/7/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09701961 BIOSIS NO.: 199598156879
Gene expression in chronic liver diseases.
AUTHOR: Petrovic L M(a); Ljubimova J Y; Demetriou A A; Geller S A
AUTHOR ADDRESS: (a)Dep. Pathol., Cedars-Sinai Med. Cent., Los Angeles, CA** USA
JOURNAL: Modern Pathology 8 (1):p141A %%%1995%%%
CONFERENCE/MEETING: Annual Meeting of the United States and Canadian Academy of Pathology Toronto, Ontario, Canada March 11-17, 1995
ISSN: 0893-3952
RECORD TYPE: Citation
LANGUAGE: English

8/7/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09352960 BIOSIS NO.: 199497361330
Role of %%%scatter%%% %%%factor%%% in the pathogenesis of AIDS-related Kaposi sarcoma.
AUTHOR: Naidu Yathi M; Rosen Eliot M; Zitnick Ralph; Goldberg Itzhak; Park Morag; Naujokas Monica; Polverini Peter J; Nickoloff Brian J(a)
AUTHOR ADDRESS: (a)Dep. Pathol., Univ. Michigan Med. Sch., M4232 Med. Sci. I, 1301 Catherine St., Ann Arbor, MI 481**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 91 (12):p5281-5285 %%%1994%%%
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Kaposi sarcoma (KS) is a complex multicellular neoplasm that is commonly associated with AIDS. The pathogenesis of KS is not well understood. KS tumor cells grow poorly in vitro and require medium conditioned by retrovirus-%%%infected%%% T lymphocytes. We observed that conditioned medium (CM) from type II human T-cell leukemia virus (HTLV-II)%%%infected%%% T cells (HTLV-II CM) induces conversion of endothelial cells (ECs) to a KS tumor cell-like phenotype. ECs grown in HTLV-II CM acquired a spindle-shaped morphology, the ability to express factor XIIIa and other KS cell markers, and a cytokine production profile similar to that of KS cells. We found that HTLV-II CM contains large quantities of %%%scatter%%% %%%factor%%% (SF), an angiogenic cytokine that stimulates cell motility. SF induced ECs to become spindle-shaped and express factor XIIIa. Moreover, SF was found to be a mitogen for KS cells in vitro and was identified within KS lesions in vivo. SF mRNA was present in KS cells in vitro, and antibodies against SF inhibited the growth of KS cells. The receptor for SF, the c-met protein, was expressed by ECs, dermal dendrocytes, and KS tumor cells in vitro and in vivo. HTLV-II CM was highly angiogenic in vivo, which was blocked by antibodies against SF. Based on these findings, we suggest that SF plays a role in the initiation and maintenance of KS lesions.

8/7/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09258627 BIOSIS NO.: 199497266997
Ultrastructural location of human hepatocyte growth factor in human liver.
AUTHOR: Sakaguchi Hiroki; Seki Shuichi; Tsubouchi Hirohito; Daikuhara Yasushi; Niitani Yoshiyuki; Kobayashi Kenzo
AUTHOR ADDRESS: Third Dep. Internal Med., Osaka City Univ. Med. Cent., 1-5-7 Asahimachi, Abeno, Osaka 545**Japan
JOURNAL: Hepatology 19 (5):p1157-1163 %%%1994%%%
ISSN: 0270-9139
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Human hepatocyte growth factor has been purified from the plasma of patients with fulminant liver failure, but where this factor is produced in organs or cells of subjects with liver diseases is unknown. Therefore, we used a monoclonal antibody to human hepatocyte growth factor to stain cells in three normal and 29 diseased liver tissues by immunohistochemical techniques. By light microscopy, the immunostained cells seemed to be polymorphonuclear leukocytes because of their segmented nuclei. Some biliary epithelial cells also were stained. Electron microscopy confirmed that the immunostained cells with segmented nuclei were polymorphonuclear leukocytes and that the stained grains were on the membranes of rough endoplasmic reticulum, around specific or azurophilic granules and in the cell sap. Stained grains in the biliary epithelial cells were found sporadically on the inside and outside of the membranes of rough endoplasmic reticulum near the nuclei. Human hepatocyte growth factor is now known to be the same protein as %%%scatter%%% %%%factor%%% and %%%tumor%%% %%%cytotoxic%%% %%%factor%%%, both of which are produced by human fibroblasts in culture, but our results suggest that polymorphonuclear leukocytes in diseased livers are one cellular source of circulating human hepatocyte growth factor. The immunostaining properties of biliary epithelial cells in diseased livers also suggest that the cells produce and secrete human hepatocyte growth factor.

8/7/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08945803 BIOSIS NO.: 199396097304
Expression and characterization of biologically active human hepatocyte growth factor (HGF) by insect cells %%%infected%%% with HGF-recombinant baculovirus.
AUTHOR: Yee Cindy J; Defrances Marie C; Bell Aaron; Bowen William; Petersen Bryon; Michalopoulos George K; Zarnegar Reza(a)
AUTHOR ADDRESS: (a)Dep. Pathology, Div. Cellular Molecular Pathology Sch. Med., Univ. Pittsburgh, Pittsburgh, PA 15**USA
JOURNAL: Biochemistry 32 (31):p7922-7931 %%%1993%%%
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A cDNA containing the entire coding sequence of human hepatocyte growth factor (HGF) (also known as %%%scatter%%% %%%factor%%% (SF)) was inserted into the genome of Autographa california nuclear polyhedrosis virus (baculovirus) adjacent to the polyhedrin promoter by homologous recombination. Insect cells (Spodoptera frugiperda) %%%infected%%% with the recombinant virus secrete relatively high levels (3-8 mg/L) of biologically active HGF into the culture medium. The recombinant HGF induces pronounced morphological changes and scattering of primary cultures of rat, mouse, and human hepatocytes within 24 h after plating and stimulates DNA synthesis in these cells with the same magnitude as native HGF derived from human placenta or rabbit serum. The human recombinant HGF produced by the insect cells is N-glycosylated, binds to heparin like native HGF, and is recognized by polyclonal antiserums raised against human or rabbit HGF as assessed by immunoblot, ELISA, and immunoneutralization experiments. Metabolic radiolabeling with L-(35S)methionine (pulse-chase experiments) as well as Western blot analysis indicates that the recombinant HGF is synthesized and secreted by the %%%infected%%% insect cells as the unprocessed single-chain form (pro-HGF) when the cells are cultured in serum-free medium. However, when the %%%infected%%% insect cells are cultured in insect culture medium (Grace's medium) containing fetal bovine serum, the secreted HGF is present mainly in the mature heterodimeric form. Addition of serum to the baculovirus-expressed single-chain (125I)HGF in a cell-free system results in conversion to the heterodimeric two-chain form, and the activation is prevented by the serine protease inhibitor PMSF. Incubation of 125I-labeled pro-HGF with rat liver or spleen extracts resulted in conversion of pro-HGF to the heterodimeric two-chain form. A truncated form of HGF containing the N-terminal portion of HGF (kringles 1-3) was also produced in the same expression system. This deleted HGF, by itself, did not have any detectable biological activity; however, it abrogated the stimulatory effects of full-length HGF on hepatocytes. This is the first successful production of bioactive recombinant HGF in large quantities, which will allow purification on the milligram scale of pro-HGF and will permit future studies to elucidate pathways involved in HGF activation by its target tissues.

8/7/18 (Item 18 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

08738128 BIOSIS NO.: 199395027479
Met and hepatocyte growth factor/%%%scatter%%% %%%factor%%% signal
transduction in normal melanocytes and melanoma cells.
AUTHOR: Halaban Ruth(a); Rubin Jeffrey S; Funasaka Yoko; Cobb Melanie; Boulton Teri; Faletto Donna; Rosen Eliot; Chan Andrew; Yoko Karen; et al
AUTHOR ADDRESS: (a)Dep. Dermatology, Yale Univ. Sch. Med., 333 Cedar Street, P.O. Box 3333, New Haven, Conn. 06510**USA
JOURNAL: Oncogene 7 (11):p2195-2206 %%%1992%%%
ISSN: 0950-9232
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The proto-oncogene c-MET encodes a transmembrane tyrosine kinase
receptor for hepatocyte growth factor/%%%scatter%%% %%%factor%%%
(HGF/SF). HGF/SF stimuates the proliferation and motility of various cell types. Because HGF/SF is also a melanocyte mitogen, we investigated the biological role of HGF/SF, including c-Met expression, activation and signal transduction, in normal and malignant human melanocytes. We show that HGF/SF is mitogenic in the presence of synergistic factors, such as basic fibroblast growth factor (bFGF) and mast cell growth factor (MGF) and that, by itself, it stimulates the motility of normal human melanocytes. The ligand also maitained high levels of tyrosinase activity and melanin content in these cells. Signal transduction by HGF/SF included phosphorylation of tyrosyl residues on c-Met, a cascade of tyrosine phosphorylations on several other proteins and activation of microtubule-associated protein kinase/extracellular signal-regulated kinase. Met expression and activity are normal in human melanomas, and constitutive activity of HGF/SF in retrovirally %%%infected%%% autonomously proliferative mouse melanocytes is insufficient to confer the malignant phenotype. Our findings suggest that activation of Met in response to HGF/SF may contribute to malignant progression synergistically with the aberrant expression of bFGF in malignant melanocytes and that, in addition, the peptide may promote dispersion of factor-dependent melanocytes from early stages of primary melanomas to ectopic sites.

8/7/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08706073 BIOSIS NO.: 199345124148
%%%Scatter%%% %%%factor%%% (SF) induces transdifferentiation of endothelial
cells (ECs) and growth of Kaposi's sarcoma (KS) cells.
AUTHOR: Nickoloff B J(a); Naidu Y; Nestle F O; Zitnick R; Goldberg I; Park M; Polverini P; Rosen E
AUTHOR ADDRESS: (a)Dep. Pathol., Univ. Mich., Long Island Jewish Med. Cent., Ann Arbor, MI**USA
JOURNAL: Clinical Research 41 (3):p691A %%%1993%%%
CONFERENCE/MEETING: Joint Meeting of the Central Society for Clinical Research, Midwest Section of the American Federation for Clinical Research and Central Region of the Society for Investigative Dermatology Chicago, Illinois, USA November 3-5, 1993
ISSN: 0009-9279
RECORD TYPE: Citation
LANGUAGE: English

8/7/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05203762 BIOSIS NO.: 000082044384
A MONOSACCHARIDE PRECURSOR OF ESCHERICHIA-COLI LIPID A HAS THE ABILITY TO
INDUCE %%%TUMOR%%%-%%%CYTOTOXIC%%% %%%FACTOR%%% PRODUCTION BY A MURINE
MACROPHAGE-LIKE CELL LINE J-774.1
AUTHOR: AMANO F; NISHIJIMA M; AKAMATSU Y
AUTHOR ADDRESS: DEPARTMENT OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH,
10-35 KAMIOTOSAKI 2-CHOME, SHINAGAWA-KU, TOKYO 141, JAPAN.
JOURNAL: J IMMUNOL 136 (11). 1986. 4122-4127. %%%1986%%%
FULL JOURNAL NAME: Journal of Immunology
CODEN: JOIMA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A monosaccharide precursor of Escherichia coli lipid A, designated lipid X, which is a diacylglucosamine 1-phosphate with .beta.-hydroxymyristoyl groups at positions 2 and 3, was shown to have the ability to induce the production of tumor necrosis factor (TNF)-like %%%tumor%%%-%%%cytotoxic%%% %%%factor%%% by a murine macrophage-like cell
line, J774.1. This cytotoxic factor was released from J774.1 cells grown in the presence of lipid X and related compounds, and it was assayed as to its lytic activity against [3H]thymidine-labeled L929 cells. Dose-response studies revealed that lipid X induced the production of smaller amounts of the %%%tumor%%%-%%%cytotoxic%%% %%%factor%%% than LPS
at low concentrations, but it induced that of considerable amounts at and over 1 .mu.g/ml. Elimination of 1-phosphate or
3-O-.beta.-hydroxymyristoyl group from lipid X completely prevented the induction of producing this factor by the macrophages. Therefore, it is suggested that both 1-phosphate and 3-O-.beta.-hydroxymyristoyl groups are essential for the biologic activity of lipid X, as to the induction of the %%%tumor%%%-%%%cytotoxic%%% %%%factor%%% production in the
macrophages.

8/7/21 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07553706 Genuine Article#: 180UG Number of References: 31
Title: Gene transfer to human pancreatic endocrine cells using viral vectors
Author(s): Leibowitz G; Beattie GM; Kafri T; Cirulli V; Lopez AD; Hayek A; Levine F (REPRINT)
Corporate Source: UNIV CALIF SAN DIEGO,SCH MED, CTR MOL GENET, WHITTIER
INST/LA JOLLA//CA/92093 (REPRINT); UNIV CALIF SAN DIEGO,SCH MED, CTR
MOL GENET, WHITTIER INST/LA JOLLA//CA/92093; UNIV CALIF SAN DIEGO,SCH
MED, DEPT PEDIAT, WHITTIER INST/LA JOLLA//CA/92093; SALK INST BIOL
STUDIES,GENET LAB/LA JOLLA//CA/
Journal: DIABETES, %%%1999%%%, V48, N4 (APR), P745-753
ISSN: 0012-1797 Publication date: 19990400
Publisher: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314
Language: English Document Type: ARTICLE
Abstract: We have studied the factors that influence the efficiency of %%%infection%%% of human fetal and adult pancreatic endocrine cells with adenovirus, murine retrovirus, and lentivirus vectors all expressing the green fluorescent protein (Ad-GFP, MLV-GFP, and Lenti-GFP, respectively). Adenoviral but not retroviral vectors efficiently %%%infected%%% intact pancreatic islets and fetal islet-like cell clusters (ICCs) in suspension. When islets and ICCs were plated in monolayer culture, %%%infection%%% efficiency with all three viral vectors increased. Ad-GFP %%%infected%%% 90-95% of the cells, whereas %%%infection%%% with MLV-GFP and Lenti-GFP increased only slightly. Both exposure to hepatocyte growth factor/%%%scatter%%%
%%%factor%%% (HGF/SF) and dispersion of the cells by removal from the
culture dish and replating had substantial positive effects on the efficiency of %%%infection%%% with retroviral vectors. Studies of virus entry and cell replication revealed that cell dispersion and stimulation by HGF/SF may be acting through both mechanisms to increase
the efficiency of retrovirus-mediated gene transfer. Although HGF/SF

and cell dispersion increased the efficiency of %%%infection%%% with
MLV-GFP, only rare cells with weak staining for insulin were
%%%infected%%%, whereas similar to 25% of beta-cells were
%%%infected%%% with Lenti-GFP. We conclude that adenovirus is the
most
potent vector for ex vivo overexpression of foreign genes in adult
endocrine pancreatic cells and is the best vector for applications
where high-level but transient expression is, desired. Under the
optimal conditions of cell dispersion plus HGF/SF, %%%infection%%%
with
MLV and lentiviral vectors is reasonably efficient and stable, but only
lentiviral vectors efficiently %%%infect%%% pancreatic beta-cells.

8/7/22 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07533982 Genuine Article#: 178HF Number of References: 31
Title: Stromal-epithelial interactions in the cornea
Author(s): Wilson SE (REPRINT) ; Liu JJ; Mohan RR
Corporate Source: UNIV WASHINGTON,DEPT OPHTHALMOL, BOX
356485, RM RR801
HSB/SEATTLE//WA/98195 (REPRINT)
Journal: PROGRESS IN RETINAL AND EYE RESEARCH, %%%1999%%%,
V18, N3 (MAY), P
293-309
ISSN: 1350-9462 Publication date: 19990500
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD,
LANGFORD LANE,
KIDLINGTON, OXFORD OX5 1GB, ENGLAND
Language: English Document Type: ARTICLE
Abstract: Stromal-epithelial interactions are key determinants of corneal
function. Bi-directional communications occur in a highly coordinated
manner between these corneal tissues during normal development,
homeostatis, and wound healing. The best characterized stromal to
epithelial interactions in the cornea are mediated by the classical
paracrine mediators hepatocyte growth factor (HGF) and keratinocyte
growth factor (KGF). HGF find KGF are produced by the keratocytes to
regulate proliferation, motility, differentiation, and possibly other
functions, of epithelial cells. Other cytokines produced by keratocytes
may also contribute to three interactions. Epithelial to stromal
interactions are mediated by cytokines, such as interleukin-l (IL-1)
and soluble Fas ligand, that are released by corneal epithelial cells
in response to injury. Other, yet to be identified, cytokine systems
may be released from the unwounded corneal epithelium to regulate
keratocyte viability and function. IL-I appears to be a master
regulator of corneal wound healing that modulates functions such as
matrix metalloproteinase production, HGF and KGF production, and
apoptosis of keratocyte cells following injury. The Fas/Fas ligand
system has been shown to contribute to the immune privileged status of
the cornea. However, this cytokine-receptor system probably also
modulates corneal cell apoptosis following %%%infection%%% by viruses
such as herpes simplex and wounding. Pharmacologic control of stromal
epithelial interactions appears to offer the potential to regulate
corneal wound healing and, possibly, treat corneal diseases in which
these interactions have a central role. (C) 1998 Elsevier Science Ltd.
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8/7/23 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07440410 Genuine Article#: 165XA Number of References: 46
Title: Elevated serum concentrations of hepatocyte growth factor in acute
myelocytic leukaemia
Author(s): HjorthHansen H (REPRINT) ; Seidel C; Lamvik J; Borset M;
Sundan
A; Waage A
Corporate Source: NORWEGIAN UNIV SCI & TECHNOL,INST CANC RES
& MOL BIOL,
NTNU/N-7005 TRONDHEIM//NORWAY/ (REPRINT); NORWEGIAN
UNIV SCI &
TECHNOL,INST INTERNAL MED, NTNU, SECT HEMATOL/N-7005
TRONDHEIM//NORWAY/
Journal: EUROPEAN JOURNAL OF HAEMATOLOGY, %%%1999%%%, V62,
N2 (FEB), P
129-134
ISSN: 0902-4441 Publication date: 19990200
Publisher: MUNKSGAARD INT PUBL LTD, 35 NORRE SOGADE, PO BOX
2148, DK-1016
COPENHAGEN, DENMARK
Language: English Document Type: ARTICLE
Abstract: Serum concentrations of hepatocyte growth factor (HGF) were
measured in 60 patients suffering from acute myelocytic leukaemia
(AML). At the time of diagnosis elevated HGF concentrations (>1.25
ng/ml) were found in 28% of the patients. HGF levels correlated with
the presence of disseminated intravascular coagulation (DIC), levels of
lysozyme, creatinine, peripheral blood blast counts and lactic
dehydrogenase. In the group of patients with high HGF (>1.25 ng/ml) we
found a tendency towards an increased early mortality; 41% of them died
within 15 d from diagnosis, as opposed to 5% of the patients with
normal HGF (log rank test p = 0.07). DIG-related bleeding or thrombosis
contributed to this early mortality. In responders, HGF levels
normalized after treatment. HGF levels are low in neutropenia and
neutropenic %%%infections%%%.

8/7/24 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07401815 Genuine Article#: 161DX Number of References: 30
Title: Hepatocyte growth factor gene therapy of liver cirrhosis in rats
Author(s): Ueki T; Kaneda Y; Tsutsui H; Nakanishi K; Sawa Y; Morishita R;
Matsumoto K; Nakamura T; Takahashi H; Okamoto E; Fujimoto J
(REPRINT)
Corporate Source: HYOGO MED UNIV,DEPT SURG 1, 1-1
MUKOGAWACHO/NISHINOMIYA/HYOGO 6638501/JAPAN/
(REPRINT); HYOGO MED
UNIV,DEPT SURG 1/NISHINOMIYA/HYOGO 6638501/JAPAN/;
OSAKA UNIV,SCH MED,
INST CELLULAR & MOL BIOL/SUITA/OSAKA 5650871/JAPAN/;
HYOGO MED
UNIV,DEPT IMMUNOL & MED
ZOOL/NISHINOMIYA/HYOGO/JAPAN/; OSAKA UNIV,SCH
MED, DEPT SURG 1/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,SCH
MED, DEPT
GERIATR MED/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,SCH MED,
BIOMED RES
CTR/SUITA/OSAKA 565/JAPAN/; MASSACHUSETTS GEN
HOSP,GASTROINTESTINAL
UNIT/BOSTON//MA/02114; HARVARD UNIV,SCH
MED/BOSTON//MA/02114
Journal: NATURE MEDICINE, %%%1999%%%, V5, N2 (FEB), P226-230
ISSN: 1078-8956 Publication date: 19990200
Publisher: NATURE AMERICA INC, 345 PARK AVE SOUTH, NEW YORK,
NY 10010-1707
Language: English Document Type: ARTICLE
Abstract: Liver cirrhosis is the irreversible end result of fibrous
scarring and hepatocellular regeneration, characterized by diffuse
disorganization of the normal hepatic structure of regenerative nodules
and fibrotic tissue(1). It is associated with prominent morbidity and
mortality, and is induced by many factors, including chronic hepatitis
virus %%%infections%%%, alcohol drinking and drug abuse. Hepatocyte
growth factor (HGF), originally identified and cloned as a potent
mitogen for hepatocytes(2-5), shows mitogenic, motogenic and
morphogenic activities for a wide variety of cells(6-9). Moreover, HGF
plays an essential part in the development and regeneration of the
liver(6.7.10), and shows anti-apoptotic activity in hepatocytes(11). In
a rat model of lethal liver cirrhosis produced by dimethylnitrosamine
administrations, repeated transfections of the human HGF gene into
skeletal muscles induced a high plasma level of human as well as
enodogenous rat HGF, and tyrosine phosphorylation of the c-Met/HGF
receptor. Transduction with the HGF gene also suppressed the increase
of transforming growth factor-beta 1 (TGF-beta 1), which plays an
essential part in the progression of liver cirrhosis, inhibited
fibrogenesis and hepatocyte apoptosis, and produced the complete
resolution of fibrosis in the cirrhotic liver, thereby improving the
survival rate of rats with this severe illness. Thus, HGF gene therapy
may be potentially useful for the treatment of patients with liver

cirrhosis, which is otherwise fatal and untreatable by conventional therapy.

8/7/25 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07209218 Genuine Article#: 137AW Number of References: 54
Title: Influence of cell polarity on retrovirus-mediated gene transfer to differentiated human airway epithelia
Author(s): Wang GS; Davidson BL; Melchert P; Slepushkin VA; vanEs HHG; Bodner M; Jolly DJ; McCray PB (REPRINT)
Corporate Source: UNIV IOWA HOSP & CLIN,DEPT PEDIAT, 200 HAWKINS DR/IOWA
CITY//IA/52242 (REPRINT); UNIV IOWA,COLL MED, DEPT PEDIAT/IOWA
CITY//IA/52242; UNIV IOWA,COLL MED, DEPT INTERNAL MED/IOWA
CITY//IA/52242; CHIRON TECHNOL CTR GENE THERAPY,/SAN DIEGO//CA/92121
Journal: JOURNAL OF VIROLOGY, %%%1998%%%, V72, N12 (DEC), P9818-9826
ISSN: 0022-538X Publication date: 19981200
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW,
WASHINGTON, DC 20005-4171
Language: English Document Type: ARTICLE
Abstract: Gene transfer with recombinant murine leukemia viruses (MuLV) provides the potential to permanently correct inherited lung diseases, such as cystic fibrosis (CF). Several problems prevent the application of MuLV-based recombinant retroviruses to lung gene therapy: (i) the lack of cell proliferation in mature pulmonary epithelia, (ii) inefficient gene transfer with a vector applied to the apical surface, and (iii) low titers of many retroviral preparations. We found that keratinocyte growth factor (KGF) stimulated proliferation of differentiated human tracheal and bronchial epithelia. Approximately 50% of epithelia divided in response to KGF as assessed by bromodeoxyuridine histochemistry. In airway epithelia stimulated to divide with KGF, high-titer ampho- and xenotropic enveloped vectors preferentially %%%infected%%% cells from the basal side. However, treatment with hypotonic shock or EGTA transiently increased transepithelial permeability, enhancing gene transfer with the vector applied to the mucosal surfaces of KGF-stimulated epithelia. Up to 35% of cells expressed the transgene after gene transfer. By using this approach, cells throughout the epithelial sheet, including basal cells, were targeted. Moreover, the Cl- transport defect in differentiated CF airway epithelia was corrected. These findings suggest that barriers to apical %%%infection%%% with MuLV can be overcome.

8/7/26 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07177820 Genuine Article#: 132TH Number of References: 25
Title: Hepatocyte growth factor (HGF) in patients with pneumonia: A comparison between survivors and non-survivors
Author(s): Nayeri F (REPRINT) ; Nilsson I; Skude G; Brudin L; Soderstrom C
Corporate Source: LINKOPING UNIV HOSP,DEPT INFECT DIS/S-58185
LINKOPING//SWEDEN/ (REPRINT); CTY HOSP,DEPT INFECT DIS/KALMAR//SWEDEN/;
CTY HOSP,DEPT CLIN CHEM/KALMAR//SWEDEN/; CTY HOSP,DEPT CLIN
PHYSIOL/KALMAR//SWEDEN/
Journal: SCANDINAVIAN JOURNAL OF INFECTIOUS DISEASES, %%%1998%%%, V30, N4
, P405-409
ISSN: 0036-5548 Publication date: 19980000
Publisher: SCANDINAVIAN UNIVERSITY PRESS, PO BOX 2959 TOYEN, JOURNAL
DIVISION CUSTOMER SERVICE, N-0608 OSLO, NORWAY
Language: English Document Type: ARTICLE
Abstract: Hepatocyte growth factor (HGF) is a multifunctional growth factor. After lung injury HGF is secreted in the lung and promotes reconstruction of the damaged organ. We measured, retrospectively, the serum HGF concentrations collected on admission in 55 patients with %%%bacterial%%% pneumonia, using an enzyme-linked immunosorbent assay
(ELISA). The patients were divided into 3 groups: Group 1 was survivors with normal liver function (ir = 14), Group 2 was survivors with abnormal Liver function (n = 31) and Group 3 was non-survivors (n = 10). Median concentrations of HGF were elevated in Groups 1 and 2; and no statistically significant difference between these 2 groups was found. Group 3 had a median HGF concentration within the reference range, significantly lower than both Group 1 and Group 2. In addition LDH was significantly higher in pen-survivors as compared with survivors. The combination of LDH and HGF concentrations discriminated between survivors and non-survivors (sensitivity 0.90 and specificity 0.96). The results support the hypothesis that increased levels of HGF might be a natural part of the healing process of lung injury, irrespective of liver involvement, and that patients without increased HGF levels, especially those with concomitant liver function impairment, may have a poor prognosis.

8/7/27 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06879286 Genuine Article#: ZY718 Number of References: 44
Title: Serum interleukin-6, interleukin-8, hepatocyte growth factor, and nitric oxide changes during thoracic surgery
Author(s): Yamada T; Hisanaga M; Nakajima Y; Kanehiro H; Watanabe A; Ohyama
T; Nishio K; Sho M; Nagao M; Harada A; Matsushima K; Nakano H (REPRINT)
Corporate Source: NARA MED UNIV,DEPT SURG 1, 840 SHIJO CHO/KASHIHARA/NARA
634/JAPAN/ (REPRINT); NARA MED UNIV,DEPT SURG 1/KASHIHARA/NARA
634/JAPAN/; UNIV TOKYO,SCH MED, DEPT MOL PREVENT MED, BUNKYO KU/TOKYO
113//JAPAN/
Journal: WORLD JOURNAL OF SURGERY, %%%1998%%%, V22, N8 (AUG), P783-790
ISSN: 0364-2313 Publication date: 19980800
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010
Language: English Document Type: ARTICLE
Abstract: Thoracic surgery creates a different environment from abdominal surgery in respect to the surgical procedure with pulmonary collapse under unilateral ventilation. Definitive evidence whether surgical trauma during thoracotomy is involved in postoperative pulmonary %%%infections%%% has not been clearly demonstrated. The objectives of this study were to evaluate the influence of surgical trauma during thoracotomy on postoperative %%%infections%%% and to investigate the clinical significance of postoperative humoral mediators in pulmonary %%%infections%%% after surgery. We measured serum interleukin-6 (IL-6),
IL-8, hepatocyte growth factor (HGF), and nitric oxide (NO) levels in 27 patients undergoing thoracic surgery; the measurements were before and during thoracotomy, 60 minutes after reinflation, and after surgery. The patients were divided into three groups: lobectomy patients (group A), and esophagectomy patients without (group B) or with (group C) postoperative %%%infections%%%. The serum IL-6 and IL-8
levels in group C were markedly elevated 60 minutes after reinflation and were significantly higher than those in group A. The serum IL-8 levels during that period in group C were significantly higher than those in group B. The postoperative serum IL-6, IL-8, HGF, and NO levels were significantly higher in group C than in group B. Taken together, intraoperative hypercytokinemia, especially IL-8, following the thoracic procedure and subsequent reinflation preceded the clinical onset of postoperative %%%infections%%%. Hence postoperative serum IL-6, IL-8, and HGF levels may be useful predictors of %%%infection%%%
after esophagectomy.

8/7/28 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06858657 Genuine Article#: ZX209 Number of References: 23
Title: Lipoteichoic acid and protein-A from Staphylococcus aureus stimulate release of hepatocyte growth factor (HGF) by human dermal fibroblasts
Author(s): Baroni A; Perfetto B; Ruocco E; Rossano F (REPRINT)
Corporate Source: UNIV NAPLES,FAC MED & CHIRURG 2, IST MICROBIOL, LARGHETTO
SANTANIELLO CAPONAPOLI 2/I-80137 NAPLES//ITALY/ (REPRINT); UNIV
NAPLES,FAC MED & CHIRURG 2, IST MICROBIOL/I-80137 NAPLES//ITALY/; UNIV
NAPLES,FAC MED & CHIRURG 2, IST CLIN DERMOSIFILOPAT/I-80137
NAPLES//ITALY/
Journal: ARCHIVES OF DERMATOLOGICAL RESEARCH, %%%1998%%%, V290, N4 (APR), P
211-214
ISSN: 0340-3696 Publication date: 19980400
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010
Language: English Document Type: ARTICLE
Abstract: In this study we demonstrated that Staphylococcus aureus lipoteichoic acid (LTA) and protein-A (PA) induce the release from human dermal fibroblasts of hepatocyte growth factor (HGF), a proliferation factor of epithelial cells (including keratinocytes). In contrast, LPS and porins from Pseudomonas aeruginosa did not stimulate HGF production. Recombinant human IL-1 beta induced HGF release. This production was synergistically enhanced when in association with LTA (by more than twice) and PA (by about two-thirds). Controls were performed in the presence of %%%bacterial%%% components alone. In previous studies we have shown that LPS and porins are inducers of IL-1 alpha and beta and other cytokines from human monocytes, Therefore it is possible that in inflammatory cutaneous foci and %%%infected%%% wounds, %%%bacterial%%% components may induce HGF release from dermal
human fibroblasts, LTA and PA act directly, while LPS and porins act indirectly, through the release of cytokines by monocytes/macrophages, HGF plays an important role in the repair of cutaneous tissue during gram-positive and gram-negative %%%infections%%%.

8/7/29 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06343195 Genuine Article#: YK655 Number of References: 54
Title: Simultaneous or delayed administration of hepatocyte growth factor equally represses the fibrotic changes in murine lung injury induced by bleomycin - A morphologic study
Author(s): Yaekashiwa M (REPRINT) ; Nakayama S; Ohnuma K; Sakai T; Abe T;
Satoh K; Matsumoto K; Nakamura T; Takahashi T; Nukiwa T
Corporate Source: TOHOKU UNIV,INST DEV AGING & CANC, DIV CANC CONTROL, DEPT
RESP ONCOL & MOL MED/SENDAI/MIYAGI 98077/JAPAN/ (REPRINT); TOHOKU
UNIV,INST DEV AGING & CANC, DEPT PATHOL, DIV ORGAN
PATHOPHYSIOL/SENDAI/MIYAGI 98077/JAPAN/; OSAKA UNIV,SCH MED, BIOMED RES
CTR, DEPT ONCOL, DIV BIOCHEM/OSAKA 553//JAPAN/
Journal: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE,
%%%1997%%%, V156, N6 (DEC), P1937-1944
ISSN: 1073-449X Publication date: 19971200
Publisher: AMER LUNG ASSOC, 1740 BROADWAY, NEW YORK, NY 10019
Language: English Document Type: ARTICLE
Abstract: Hepatocyte growth factor (HGF) is a humoral mediator of epithelial-mesenchymal interactions, acting on a variety of epithelial cells as mitogen, motogen, and morphogen. Exogenous HGF acts as a hepatotrophic factor and a renotrophic factor during experimental injury. To investigate whether HGF has a pulmotrophic function, human recombinant HGF was administered to C57BL/6 mice with severe lung injury by bleomycin (BLM). Low dose simultaneous and continuous administration of HGF (50 mu g/mouse/7 d) with BLM (100 mg/mouse/7 d)
repressed fibrotic morphological changes at 2 and 4 wk. Ashcroft score showed a significant difference in lung fibrosis with and without HGF at 4 wk (3.7 +/- 0.4 versus 4.9 +/- 0.3, p < 0.05). Furthermore, either simultaneous or delayed administration of high dose HGF (280 mu g/mouse/14 d) equally repressed fibrotic changes by BLM when examined at 4 wk (Ashcroft score: 2.6 +/- 0.4 and 2.4 +/- 0.2 versus 4.1 +/- 0.2, p < 0.01). Hydroxyproline content in the lungs was significantly lower in mice with either simultaneous or delayed administration of high dose HGF as compared to those administered BLM alone (121.8 +/- 8.1% and 113.2 +/- 6.2% versus 162.7 +/- 4.6%, p < 0.001). These findings indicate that exogenous HGF acts as a pulmotrophic factor in vivo and prevents the progression of BLM-induced lung injury when administered in either a simultaneous or delayed fashion. HGF may be a potent candidate to prevent or treat lung fibrosis.

8/7/30 (Item 10 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06203805 Genuine Article#: BJ68B Number of References: 171
Title: Genes involved in oncogenesis
Author(s): Cortner J (REPRINT) ; VandeWoude S; VandeWoude GF
Corporate Source: NCI,NIH, DIV BASIC SCI/BETHESDA//MD/20892 (REPRINT);
COLORADO STATE UNIV,LAB ANIM RESOURCES/FT COLLINS//CO/80523; NCI,ABL
BASIC RES PROGRAM, FREDERICK CANC RES & DEV CTR/FREDERICK//MD/21702
, %%%1997%%%, V40, P51-102
Publication date: 19970000
Publisher: ACADEMIC PRESS INC, 525 B STREET, SUITE 1900, SAN DIEGO, CA
92101-4495ADVANCES IN VETERINARY MEDICINE (ACADEMIC PRESS)
Series: ADVANCES IN VETERINARY MEDICINE (ACADEMIC PRESS)
Language: English Document Type: REVIEW

8/7/31 (Item 11 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06133562 Genuine Article#: XX017 Number of References: 58
Title: Functional and biophysical characterization of recombinant human hepatocyte growth factor isoforms produced in Escherichia coli
Author(s): Stahl SJ; Wingfield PT (REPRINT) ; Kaufman JD; Pannell LK; Cioce
V; Sakata H; Taylor WG; Rubin JS; Bottaro DP
Corporate Source: NIAMSD,PROT EXPRESS LAB, NIH, BLDG 6B, ROM 1B130, 6 CTR
DR, MSC 2775/BETHESDA//MD/20892 (REPRINT); NIAMSD,PROT EXPRESS LAB,
NIH/BETHESDA//MD/20892; NIDDKD,STRUCT MASS SPECTROMETRY GRP,
LAC/BETHESDA//MD/20892; NCI,CELLULAR & MOL BIOL LAB, DIV BASIC
SCI/BETHESDA//MD/20892
Journal: BIOCHEMICAL JOURNAL, %%%1997%%%, V326, 3 (SEP 15), P763-772
ISSN: 0264-6021 Publication date: 19970915
Publisher: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON, ENGLAND W1N 3AJ
Language: English Document Type: ARTICLE
Abstract: Hepatocyte growth factor (HGF) is a pluripotent secreted protein that stimulates a wide array of cellular targets, including hepatocytes and other epithelial cells, melanocytes, endothelial and haematopoietic cells. Multiple mRNA species transcribed from a single HGF gene encode at least three distinct proteins: the full-length HGF protein and two truncated HGF isoforms that encompass the N-terminal(Nf domain through
kringle 1 (NK1) or through kringle 2 (NK2), We report the high-level expression in Escherichia call of NK1 and NK2, as well as the individual kringle 1 (K1) and N domains of HGF. All proteins accumulated as insoluble aggregates that were solubilized, folded and purified in high yield using a simple procedure that included two gelfiltration steps. Characterization of the purified proteins indicated chemical and physical homogeneity, and analysis by CD suggested native conformations, Although the K1 and N-terminal domains

of HGF have limited biological activity, spectroscopic evidence indicated that the conformation of each matched that observed when the domains were components of biologically active NK1. Both NK1 and NK2 produced in %%%bacteria%%% were functionally equivalent to proteins generated by eukaryotic systems, as indicated by mitogenicity, cell scatter, and receptor binding and activation assays. These data indicate that all four %%%bacterially%%% produced HGF derivatives are well suited for detailed structural analysis.

8/7/32 (Item 12 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06108532 Genuine Article#: XV213 Number of References: 49
Title: Role of hepatocyte growth factor in endothelial regulation: prevention of high D-glucose-induced endothelial cell death by prostaglandins and phosphodiesterase type 3 inhibitor
Author(s): Morishita R; Higaki J; Hayashi SI; Yo Y; Aoki M; Nakamura S; Moriguchi A; Matsushita H; Matsumoto K; Nakamura T; Ogihara T (REPRINT)
Corporate Source: OSAKA UNIV,SCH MED, DEPT GERIATR MED, 2-2 YAMADAOKA/SUITA/OSAKA 565/JAPAN/ (REPRINT); OSAKA UNIV,SCH MED, DEPT
GERIATR MED/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,SCH MED, BIOMED RES CTR,
DIV BIOCHEM, DEPT ONCOL/SUITA/OSAKA 565/JAPAN/
Journal: DIABETOLOGIA, %%%1997%%%, V40, N9 (SEP), P1053-1061
ISSN: 0012-186X Publication date: 19970900
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010
Language: English Document Type: ARTICLE
Abstract: Injury of endothelial cells (EC) has been postulated as the initial trigger of the progression of atherosclerosis in patients with diabetes mellitus. We previously reported that decrease in a novel endothelium-specific growth factor, hepatocyte growth factor (HGF), by high D-glucose might be a trigger of endothelial injury. However, the physiological role of the local vascular HGF system has not yet been clarified. To investigate the role of HGF in endothelial injury, we initially examined the effects of HGF on endothelial injury induced by serum deprivation. Decrease in EC number by serum deprivation was significantly attenuated by addition of HGF as well as recombinant basic fibroblast growth factor, whereas vascular endothelial growth factor showed no effect. Apoptotic changes in EC induced by serum deprivation were also significantly attenuated by addition of HGF ($p < 0.01$). Given the protective action of HGF, we next studied the physiological role of local HGF production in endothelial regulation. We focused on the protective actions of prostaglandin (PG) I-2, PGE and a phosphodiesterase type 3 inhibitor (cilostazol) on endothelial injury by high glucose, since these agents are widely used in the treatment of peripheral arterial disease which is frequently observed in diabetic patients. Treatment of human aortic EC with PGE(1), PGE(2), and a PGI(2) analogue (beraprost sodium) as well as cilostazol stimulated EC growth. HGF concentration in conditioned medium from EC treated with PGE(1), PGE(2) or PGI(2) analogue as well as cilostazol was significantly higher than that with vehicle ($p < 0.01$). Interestingly, treatment with PGI(2) analogue or cilostazol attenuated high D-glucose-induced EC death, which was abolished by neutralizing anti-HGF antibody. Moreover, decreased local HGF production by high D-glucose was also significantly attenuated by PGI(2) analogue or cilostazol. Finally, we tested the effects of PGE, PGI(2) analogue and cilostazol on local HGF production in human aortic vascular smooth muscle cells (VSMC). Although high D-glucose treatment resulted in a significant increase in VSMC number, PGI(2) analogue and/or cilostazol treatment had no effects on VSMC growth. However, the decrease in local HGF production by high D-glucose was significantly attenuated by addition of PGI(2) analogue or cilostazol.

Overall, this study demonstrated that treatment with PGE, PGI(2) analogue or cilostazol prevented aortic EC death induced by high D-glucose, probably through the activation of local HGF production. Increased local vascular HGF production by prostaglandins and cilostazol may prevent endothelial injury, potentially resulting in the improvement of peripheral arterial disease.

8/7/33 (Item 13 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05990023 Genuine Article#: XM400 Number of References: 43
Title: Proprotein-processing endoprotease furin controls growth of pancreatic beta-cells
Author(s): Kayo T; Sawada Y; Suda M; Konda Y; Izumi T; Tanaka S; Shibata H;
Takeuchi T (REPRINT)
Corporate Source: GUNMA UNIV,INST MOL & CELLULAR REGULAT, DEPT MOL MED,
SHOWAMACHI/MAEBASHI/GUMMA 371/JAPAN/ (REPRINT); GUNMA UNIV,INST MOL &
CELLULAR REGULAT, DEPT MOL MED/MAEBASHI/GUMMA 371/JAPAN/; GUNMA
UNIV,INST MOL & CELLULAR REGULAT, DEPT CELL BIOL/MAEBASHI/GUMMA
371/JAPAN/
Journal: DIABETES, %%%1997%%%, V46, N8 (AUG), P1296-1304
ISSN: 0012-1797 Publication date: 19970800
Publisher: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314
Language: English Document Type: ARTICLE
Abstract: We have previously reported that in the well-differentiated beta-cell line MIN6 cells, the beta-cell-specific differentiated characteristics, such as insulin content, expression of prohormone convertases PC2 and PC3, and glucose-regulated insulin secretion, diminished when the proprotein-processing endoprotease furin was highly expressed. Since furin converts many growth-related protein precursors to their bioactive forms, we compared the four pancreatic islet cell lines RINm5F, beta TC3, beta HC9, and MIN6 with respect to cell growth rate, furin expression, endoprotease activity, and insulin content. RINm5F cells exhibited the strongest furin expression, higher furin-type endoprotease activity, and the fastest cell growth, but had the least insulin content. In contrast, MING cells exhibited only a weak furin expression, little furin-type endoprotease activity, and the slowest cell growth, but had the highest insulin content. To test whether furin-expressing cells secrete growth-promoting factors cleaved by furin, we prepared conditioned media from RINm5F and furin cDNA-introduced MING (MING-F) cells. The conditioned media from RINm5F
and MIN6-F induced increased DNA synthesis and promoted the growth of
normal MIN6 cells, compared with the medium from the empty vector-introduced MIN6-0 cells. We then examined the effect of the protease inhibitors alpha(1)-antitrypsin and its variants by %%%infecting%%% their vaccinia recombinants to the four cell lines. All conditioned media from each cell line expressing the furin-specific alpha(1)-antitrypsin variant exhibited the least DNA synthetic capacity on normal MING cells. Furthermore, all three sublines of MING-F grew faster than MIN6-0 and MING. Thus, we suggest that the islet cells with higher furin expression may induce increased production of growth factors, which result in an increase in cell growth, through an autocrine/paracrine mechanism.

8/7/34 (Item 14 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05963486 Genuine Article#: XK789 Number of References: 26
Title: Serum hepatocyte growth factor %%%scatter%%% %%%factor%%% levels in
small cell lung cancer patients
Author(s): Takigawa N (REPRINT) ; Segawa Y; Maeda Y; Takata I; Fujimoto N
Corporate Source: NATL SHIKOKU CANC CTR HOSP,DEPT MED & CLIN RES/MATSUYAMA/EHIME 790/JAPAN/ (REPRINT)
Journal: LUNG CANCER, %%%1997%%%, V17, N2-3 (JUL), P211-218
ISSN: 0169-5002 Publication date: 19970700
Publisher: ELSEVIER SCI IRELAND LTD, CUSTOMER RELATIONS MANAGER, BAY 15,
SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND
Language: English Document Type: ARTICLE
Abstract: Serum hepatocyte growth factor/%%%scatter%%%

%%%factor%%%
(HGF/SF) levels were measured in 25 patients with small cell lung cancer (SCLC), 16 patients with benign lung diseases and 15 healthy subjects with an enzyme-linked immunosorbent assay. The patients with SCLC did not have %%%bacterial%%% or interstitial pneumonia. Patients with benign lung diseases included eight with %%%bacterial%%% pneumonia, three with interstitial pneumonia, and five with benign lung tumor. Serum HGF/SF levels were significantly higher in patients with SCLC (mean +/- S.D.: 0.40 +/- 0.17 ng/ml) than in healthy subjects (0.26 +/- 0.093 ng/ml) (P = 0.0083). Patients with %%%bacterial%%% pneumonia had significantly higher serum HGF/SF (0.52 +/- 0.19 ng/ml) than did those with benign lung tumors (0.27 +/- 0.058 ng/ml) and healthy subjects (P = 0.013 and P = 0.0019, respectively). By clinical stage of SCLC, HGF/SF levels were 0.34 +/- 0.12 and 0.47 +/- 0.20 ng/ml in patients with limited disease and extensive disease, respectively; this difference was not significant (P = 0.080). Although serum HGF/SF levels were increased in patients with SCLC, this increase might not have been related to tumor burden. (C) 1997 Elsevier Science Ireland Ltd.

8/7/35 (Item 15 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05601500 Genuine Article#: WK066 Number of References: 25
Title: Increase in the circulating level of hepatocyte growth factor in gastric cancer patients
Author(s): Taniguchi T (REPRINT) ; Kitamura M; Arai K; Iwasaki Y; Yamamoto
Y; Igari A; Toi M
Corporate Source: TOKYO METROPOLITAN KOMAGOME HOSP,DEPT SURG, BUNKYO KU,
3-18-22 HONKOMAGOME/TOKYO//JAPAN/ (REPRINT); TOKYO METROPOLITAN
KOMAGOME HOSP,DEPT PATHOL, BUNKYO KU/TOKYO//JAPAN/
Journal: BRITISH JOURNAL OF CANCER, %%%1997%%%, V75, N5, P673-677
ISSN: 0007-0920 Publication date: 19970000
Publisher: CHURCHILL LIVINGSTONE, JOURNAL PRODUCTION DEPT, ROBERT STEVENSON
HOUSE, 1-3 BAXTERS PLACE, LEITH WALK, EDINBURGH, MIDLOTHIAN, SCOTLAND
EH1 3AF
Language: English Document Type: ARTICLE
Abstract: We measured serum concentrations of hapatocyte growth factor (HGF) in patients with gastric cancer and compared these with the histological findings and conventional tumour markers, including CEA, CA19-9 and CA125, for evaluation of the significance of serum HGF levels as a tumour marker. The HGF levels were measured by an enzyme-linked immunosorbent assay (ELISA) system. The average levels of
serum HGF in 89 healthy control subjects, 104 patients with primary gastric cancer and 15 patients with recurrent gastric cancer were 0.31 +/- 0.11 ng ml(-1), 0.42 +/- 0.50 ng ml(-1) and 0.92 +/- 0.39 ng ml(-1) respectively. The average level in patients with recurrent disease was significantly higher than in healthy control subjects and in primary cancer patients (P<0.001 and P<0.003 respectively). Of 104 patients with primary gastric cancer, 35 (33.7%) showed an aberrant increase in the circulating level of HGF. The increased HGF levels were significantly associated with the degrees of histological tumour invasion and venous invasion. Of 15 patients with recurrent gastric cancer, 14 (93.3%) showed an aberrant increase. No correlation was found between serum HGF levels and CEA levels, CA19-9 levels and CA125 levels. However, the rate of the aberrant increase in HGF levels was significantly higher than that of any other tumour markers, including CEA, CA19-9 and CA125, in primary gastric cancer patients. In conclusion, the circulating levels of HGF were elevated in approximately one-third of patients with primary gastric cancer, particularly in those with high grades of histological tumour invasion and venous invasion, and frequently in patients with distant metastases, suggesting that HGF might play important roles in the tumour progression of gastric cancer. Furthermore, serum HGF levels may be of value as a tumour marker in patients with gastric cancer.

8/7/36 (Item 16 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05459433 Genuine Article#: WA555 Number of References: 59
Title: THE RELATION BETWEEN REACTIVE OXYGEN SPECIES AND CYTOKINES IN
ANDROLOGICAL PATIENTS WITH OR WITHOUT MALE ACCESSORY-GLAND
%%%INFECTION%%%
Author(s): DEPUYDT CE; BOSMANS E; ZALATA A; SCHOONJANS F; COMHAIRE FH
Corporate Source: STATE UNIV GHENT HOSP,DEPT INTERNAL MED,SECT ENDOCRINOL &
METAB DIS,DE PINTELAAN 185/B-9000 GHENT//BELGIUM/; STATE UNIV GHENT
HOSP,DEPT INTERNAL MED,SECT ENDOCRINOL & METAB DIS/B-9000
GHENT//BELGIUM/; ST JANSHOSP,GENK INST FERTIL TECHNOL/B-9000
GHENT//BELGIUM/; MANSOURA UNIV/MANSOURA//EGYPT/
Journal: JOURNAL OF ANDROLOGY, %%%1996%%%, V17, N6 (NOV-DEC), P699-707
ISSN: 0196-3635
Language: ENGLISH Document Type: ARTICLE
Abstract: The presence of various cytokines, namely hepatocyte growth factor (HGF), interleukin-l receptor antagonist(Il-l RA), and interleukins (IL-1 alpha, IL-6, and IL-8), as well as the production of reactive oxygen species (ROS) was investigated in seminal plasma of fertile and infertile patients in order to evaluate the possible value of measuring these substances for the diagnosis of male accessory gland %%%infection%%%, and to assess the possible relationship between oxidative stress and cytokines during leucocytospermia and male accessory gland %%%infection%%% (MAGI). Our findings indicate that all of the measured cytokines seem to be produced locally as well as by white blood cells (WBC) and that, due to the presence of higher numbers of WBC, accessory gland %%%infection%%% may exert a deleterious effect
on sperm quality through the production of ROS and/or of particular cytokines such as IL-1 alpha, IL-1 RA, and IL-8. The most specific marker for a sensitivity of 95% in discriminating between cases with or without MAGI is the measurement of IL-6 in seminal plasma. In the absence of WBC several cytokines are constitutively produced and correlate with sperm concentration (HGF, IL-8), alpha-glucosidase (IL-6), and gamma-glutamyltransferase activity (HGF). The measurement of these cytokines in semen may provide clinically useful information for the diagnosis of male accessory gland %%%infection%%%, as well as in the absence of WBC where it can provide information about certain mechanisms of male reproductive function and dysfunction.

8/7/37 (Item 17 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05193559 Genuine Article#: VG766 Number of References: 56
Title: INTERLEUKIN-1 INDUCES AN AUTOCRINE LOOP HEPATOCYTE GROWTH-FACTOR
C-MET IN MURINE KAPOSI-LIKE SPINDLE CELLS
Author(s): MAIER JAM; MARIOTTI M; COMOGLIO PM; SORIA MR
Corporate Source: UNIV MILAN,HSR,DEPT BIOMED SCI & TECHNOL/MILAN//ITALY/;
SAN RAFFAELE SCI INST,DEPT BIOL & TECHNOL RES,DIBIT/I-20132
MILAN//ITALY/; UNIV TURIN,SCH MED,DEPT BIOMED SCI & TECHNOL/I-10126
TURIN//ITALY/
Journal: ONCOGENE, %%%1996%%%, V13, N5 (SEP 5), P1009-1015
ISSN: 0950-9232
Language: ENGLISH Document Type: ARTICLE
Abstract: Several cytokines, growth factors and the HIV transactivator Tat were shown to be involved in the pathogenesis of Kaposi's sarcoma, BKV/tat transgenic mice develop Kaposi's sarcoma-like lesions, and spindle-shaped cells (TTB) have been derived from these lesions, Here we show that TTB cells co-express hepatocyte growth factor (HGF) and its receptor, the product of the oncogene c-Met. An autocrine loop HGF/Met sustains spindle cell proliferation in vitro; indeed, an

antisense oligomer targeted against HGF markedly inhibited cell growth, Moreover, HGF and Met are overexpressed after exposing TTB cells to the proinflammatory cytokine interleukin 1 (IL-1), We argue that upon exposure to IL-1, an HGF/Met autocrine loop is induced which could explain the appearance of multiple foci of uncontrolled growth, In addition, due to its angiogenic activity, HGF may also sustain the neovascularization typical of Kaposi's sarcoma lesions.

8/7/38 (Item 18 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04758387 Genuine Article#: UF082 Number of References: 37
Title: PLASMA HEPATOCYTE GROWTH-FACTOR LEVELS ARE INCREASED IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME
Author(s): SAKON M; KITA Y; YOSHIDA T; UMESHITA K; GOTOH M; KANAI T; KAWASAKI T; KAMBAYASHI J; MONDEN M
Corporate Source: OSAKA UNIV,SCH MED,DEPT SURG 2,2-2 YAMADOAKA/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,SCH MED,DEPT SURG 2/SUITA/OSAKA 565/JAPAN/
Journal: SURGERY TODAY-THE JAPANESE JOURNAL OF SURGERY, %%%1996%%%, V26, N4, P236-241
ISSN: 0941-1291
Language: ENGLISH Document Type: ARTICLE
Abstract: Interleukin-1 (IL-1), a cytokine released from macrophages by endotoxin stimulation, has been shown to upregulate the genetic expression of the hepatocyte growth factor (HGF). The present study was conducted to determine whether plasma HGF is increased in patients with systemic inflammatory response syndrome (SIRS). The plasma levels of HGF, endotoxin, and beta-glucan were measured in 41 surgical patients without hepatic diseases, 18 of whom had been diagnosed with %%%sepsis%%%, and 33, with nonseptic SIRS. The plasma HGF was found to be significantly increased in the 18 patients with %%%sepsis%%%, at 0.69 +/- 0.47 ng/ml (mean +/- SD), and in the 23 patients with nonseptic SIRS, at 0.49 +/- 0.37 ng/ml, compared to values in 40 normal controls, at 0.10 +/- 0.03 ng/ml (P < 0.001). No significant correlations were observed between the plasma levels of HGF and endotoxin (r = 0.02) or beta-glucan (r = -0.05) in any of the patients; however, plasma HGF was significantly correlated,vith the WBC count (r = 0.34, P < 0.05) and with total bilirubin (r = 0.45, P < 0.01). Plasma HGF was also strongly correlated with alanine transaminase (ALT) in 8 patients with ALT levels higher than 50 U/l (r = 0.70), but there was no such correlation in 33 patients with ALT levels of 50 U/l or less (r = 0.30). Thus, although the clinicopathologic significance of HGF is not well understood, the present findings indicate that plasma HGF increases in response to %%%infection%%% or inflammation.

8/7/39 (Item 19 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04729634 Genuine Article#: UD418 Number of References: 220
Title: MEDIATORS, CYTOKINES, AND GROWTH-FACTORS IN LIVER LUNG INTERACTIONS
Author(s): PANOS RJ; BAKER SK
Corporate Source: NORTHWESTERN UNIV,SCH MED,DEPT MED,DIV PULM,ROOM 777,PASSAVANT PAVILION,303 E SUPER ST/CHICAGO//IL/60611; LAKESIDE VET ADM MED CTR/CHICAGO//IL/00000
Journal: CLINICS IN CHEST MEDICINE, %%%1996%%%, V17, N1 (MAR), P151&
ISSN: 0272-5231
Language: ENGLISH Document Type: REVIEW
Abstract: Multiple mediators have been implicated in the interactions between the liver and the lungs in various disease states. The best characterized mediator of liver-lung interaction is alpha(1)-antitrypsin. Several cytokines and mediators may be involved in the pathogenesis of the hepatopulmonary syndrome and in the cytokine cascades that are activated in systemic inflammatory states such as acute respiratory distress syndrome. Hepatocyte growth factor or %%%scatter%%% %%%factor%%% is a recently described peptide with a broad range of biologic effects that may mediate lung-liver interactions.

8/7/40 (Item 20 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04548224 Genuine Article#: TR245 Number of References: 21
Title: OVER-EXPRESSION OF HEPATOCYTE GROWTH-FACTOR IN HUMAN KAPOSIS-SARCOMA
Author(s): MAIER JAM; MARIOTTI M; ALBINI A; COMI P; PRAT M; COMOGLIO PM; SORIA MR
Corporate Source: UNIV MILAN,DEPT BIOMED SCI & TECHNOL HSR,58 VIAOLGETTINA/I-20132 MILAN//ITALY/; SAN RAFFAELE INST,DIBIT,DEPT BIOL & TECHNOL RES/MILAN//ITALY/; UNIV TURIN,DEPT BIOMED SCI & ONCOL/TURIN//ITALY/; NATL INST CANC RES/GENOA//ITALY/
Journal: INTERNATIONAL JOURNAL OF CANCER, %%%1996%%%, V65, N2 (JAN 17), P 168-172
ISSN: 0020-7136
Language: ENGLISH Document Type: ARTICLE
Abstract: Kaposi's sarcoma is a highly vascularized multifocal tumor which frequently appears as a complication of HIV %%%infection%%%. It has been suggested that a disorder in the cytokine network may contribute to the development of the disease. We examined the expression of several cytokines in human sporadic Kaposi's-sarcoma specimens, as well as in spindle cells cultured from human lesions, and consistently found high levels of expression of hepatocyte growth factor (HGF). In addition, human lesion-derived spindle cells synthesize and secrete biologically active hepatocyte growth factor and express the hepatocyte-growth-factor receptor (c-MET). Moreover, elevated levels of transforming growth factor beta 1 (TGF beta 1) mRNA were found in lesions of human sporadic Kaposi's sarcoma and in lesion-derived spindle cells which also over-express urokinase. Since HGF, TGF beta 1 and urokinase are all involved in capillary-vessel organization, dysregulation of these interacting agents may play a role in the initiation and/or progression of Kaposi's sarcoma, stimulating the growth of spindle cells and recruiting endothelial cells into the lesion. (C) 1996 Wiley-Liss, Inc.

8/7/41 (Item 21 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04402083 Genuine Article#: TA617 Number of References: 73
Title: GROWTH FACTOR-INDUCED TYROSINE PHOSPHORYLATION OF HRS, A NOVEL 115-KILODALTON PROTEIN WITH A STRUCTURALLY CONSERVED PUTATIVE ZINC-FINGER DOMAIN
Author(s): KOMADA M; KITAMURA N
Corporate Source: KANSAI MED UNIV,INST LIVER RES/MORIGUCHI/OSAKA 570/JAPAN/
Journal: MOLECULAR AND CELLULAR BIOLOGY, %%%1995%%%, V15, N11 (NOV), P 6213-6221
ISSN: 0270-7306
Language: ENGLISH Document Type: ARTICLE
Abstract: The activation of growth factor receptor tyrosine kinases leads to tyrosine phosphorylation of many intracellular proteins which are thought to play crucial roles in growth factor signaling pathways. We previously showed that tyrosine phosphorylation of a 115-kDa protein is rapidly induced in cells treated with hepatocyte growth factor. To clarify the structure and possible function of the 115-kDa protein (designated Hrs for hepatocyte growth factor-regulated tyrosine kinase substrate), we purified this protein from B16-F1 mouse melanoma cells by anti-phosphotyrosine immunoaffinity chromatography and determined

its partial amino acid sequences. On the basis of the amino acid sequences, we molecularly cloned the cDNA for mouse Hrs. The nucleotide sequence of the cDNA revealed that Hrs is a novel 775-amino-acid protein with a putative zinc finger domain that is structurally conserved in several other proteins. This protein also contained a proline-rich region and a proline- and glutamine-rich region. The expression of Hrs mRNA was detected in all adult mouse tissues tested and also in embryos. To analyze the Hrs cDNA product, we prepared a polyclonal antibody against %%%bacterially%%% expressed Hrs. Using this
antibody, we showed by subcellular fractionation that Hrs is localized to the cytoplasm; we also showed that that tyrosine phosphorylation of Hrs is induced in cells treated with epidermal growth factor or platelet-derived growth factor. These results suggest that Brs plays a unique and important role in the signaling pathway of growth factors.

8/7/42 (Item 22 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04275722 Genuine Article#: RT916 Number of References: 37
Title: HEPATOCYTE GROWTH-FACTOR SUPPRESSES THE ONSET OF LIVER-CIRRHOSIS AND
ABROGATES LETHAL HEPATIC-DYSFUNCTION IN RATS
Author(s): MATSUDA Y; MATSUMOTO K; ICHIDA T; NAKAMURA T
Corporate Source: OSAKA UNIV,SCH MED,BIOMED RES CTR,DEPT ONCOL,DIV
BIOCHEM,2-2 YAMADAOKA/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,SCH MED,BIOMED
RES CTR,DEPT ONCOL,DIV BIOCHEM/SUITA/OSAKA 565/JAPAN/; NIIGATA UNIV,SCH
MED,DEPT INTERNAL MED 3/NIIGATA 951//JAPAN/
Journal: JOURNAL OF BIOCHEMISTRY, %%%1995%%%, V118, N3 (SEP), P643-649
ISSN: 0021-924X
Language: ENGLISH Document Type: ARTICLE
Abstract: Hepatic fibrosis/cirrhosis is a common hepatic disease characterized by the hyper-accumulation of connective tissue components, and hepatic necrosis, Chronic alcohol ingestion, viral %%%infection%%%, and metabolic disorders are contributing factors and there has been no effective treatment, Hepatocyte growth factor (HGF), originally identified as a potent mitogen for mature hepatocytes, is a long-sought hepatotrophic factor for liver regeneration, Administration of human recombinant HGF into rats with hepatic fibrosis/cirrhosis caused by dimethylnitrosamine (DMN) elicited mitogenic action for hepatocytes, stimulated hepatic collagenase activity, and prevented the onset and progression of hepatic fibrosis/cirrhosis, Accumulation of fibrous tissue components in the liver due to DMN-treatment were markedly decreased in HGF-injected rats. Moreover, HGF completely abrogated death caused by severe hepatic cirrhosis and dysfunction, We postulate that HGF may prove to be an effective treatment for human liver fibrosis/cirrhosis and for chronic hepatic failure.

8/7/43 (Item 23 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04112126 Genuine Article#: QY953 Number of References: 90
Title: IMMUNOGOLD LABELING OF ONCOGENIC AND TUMOR-RELATED PROTEINS
Author(s): RULONG S; ZHOU RP; TSARFATY I; HUGHES S; VANDEWOUDE G; DASILVA
PP
Corporate Source: NCI,FREDERICK CANC RES & DEV CTR,ABL BASIC RES
PROGRAM,POB B,BLDG 538,RM 124/FREDERICK//MD/21702; NCI,FREDERICK CANC
RES & DEV CTR,STUCT BIOL SECT,DCBDC INTRAMURAL RES
PROGRAM/FREDERICK//MD/21702
Journal: MICROSCOPY RESEARCH AND TECHNIQUE, %%%1995%%%, V31, N2 (JUN 1), P
159-173
ISSN: 1059-910X
Language: ENGLISH Document Type: ARTICLE
Abstract: Immunogold labeling electron microscopy technique has been used to study the ultrastructural localization of oncogenic proteins: Mos, Met, Ski, and the tumor-associated protein, Muc1, as well as their relationship with other tumor-related proteins. By pre- and postembedding immunogold labeling electron microscopy techniques, we showed that the Mos protein pp39(mos) colocalized with microtubule bundles, suggesting that microtubulin or microtubule-associated protein(s) may be the substrate of Mos. Met protein was labeled at the microvilli of the lumen that are formed in cultured T47D cells, implying its potential involvement in lumen formation. Ski localization experiments revealed a unique globular structure ''Ski body'' that is present inside the nucleus of interphase chicken embryo fibroblast %%%infected%%% with Ski cDNA FB29 and FB2-29. Ski bodies were also found scattered in the cytoplasm of metaphase FB29 and FB2-29 Ski expressing chicken embryo fibroblasts. In T47D cells, tumor-associated protein Muc1 was associated with both the plasma membrane and the membranes of secretory vesicles in the cytoplasm. In MUC1 %%%infected%%% NIH3T3 cells, however, labeling showed that in addition
to the plasma membrane and the membranes of secretory vesicles, some Mud gold spheres were seen inside the secretory vesicles, suggesting that the subcellular localization of the protein may vary in different cell types. (C) 1995 Wiley-Liss, Inc.

8/7/44 (Item 24 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02127387 Genuine Article#: KD073 Number of References: 41
Title: EXPRESSION AND CHARACTERIZATION OF HEPATOCYTE GROWTH-FACTOR
RECEPTOR-IGG FUSION PROTEINS - EFFECTS OF MUTATIONS IN THE POTENTIAL
PROTEOLYTIC CLEAVAGE SITE ON PROCESSING AND LIGAND-BINDING
Author(s): MARK MR; LOKKER NA; ZIONCHECK TF; LUIS EA; GODOWSKI PJ
Corporate Source: GENENTECH INC,DEPT MOLEC BIOL,460 POINT SAN BRUNO BLVD/S
SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT CELL GENET/S SAN
FRANCISCO//CA/94080; GENENTECH INC,DEPT METAB/S SAN FRANCISCO//CA/94080
; GENENTECH INC,DEPT CARDIOVASC RES/S SAN FRANCISCO//CA/94080
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, %%%1992%%%, V267, N36 (DEC 25), P
26166-26171
ISSN: 0021-9258
Language: ENGLISH Document Type: ARTICLE
Abstract: The receptor for hepatocyte growth factor (HGF) is the product of
the c-met proto-oncogene, a membrane-spanning tyrosine kinase receptor. To facilitate analysis of HGF and its receptor (HGFr), we expressed and purified a chimeric protein containing the extracellular domain (ECD) of the HGFr fused to the constant region of IgG heavy chain. This soluble form of the HGFr (sHGFr) bound HGF with an affinity similar to that of the authentic, membrane-associated receptor. The sHGFr also neutralized the binding of HGF to the HGFr expressed on A549 cells. Like the mature form of the HGFr, sHGFr is a heterodimer which arises by proteolytic processing within the ECD. In order to characterize the requirements for proteolytic processing of the ECD and the effects of cleavage on ligand binding, we expressed sHGFr variants containing amino acid substitutions in the putative processing site. Replacement of the P1 or P4 arginine, but not the P3 lysine, with alanine inhibited conversion to the alpha/beta heterodimer. This suggests that maturation is mediated by furin or a furin-like protease. Finally, we showed that processing of the sHGFr into the alpha/beta form is not required for high affinity binding to either pro- or mature HGF.

8/7/45 (Item 25 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01242919 Genuine Article#: GH250 Number of References: 38

Title: TUMOR-NECROSIS-FACTOR STIMULATES EPITHELIAL TUMOR-CELL MOTILITY
Author(s): ROSEN EM; GOLDBERG ID; LIU D; SETTER E; DONOVAN MA; BHARGAVA M;
REISS M; KACINSKI BM
Corporate Source: YALE UNIV,SCH MED,DEPT THERAPEUT RADIOL,132 HRT,333 CEDAR
ST/NEW HAVEN//CT/06510; YALE UNIV,SCH MED,DEPT MED,DIV MED ONCOL/NEW
HAVEN//CT/06510; LONG ISL JEWISH MED CTR,DEPT RADIAT ONCOL/NEW HYDE
PK//NY/11042; CETUS CORP/EMERYVILLE//CA/94608
Journal: CANCER RESEARCH, %%%1991%%%, V51, N19, P5315-5321
Language: ENGLISH Document Type: ARTICLE
Abstract: Cellular motility is a critical function in embryonic development, tissue repair, and tumor invasion. We used assays of scattering (epithelial colony dispersion), cell migration, and cell invasion to study cytokine-regulated motility in epithelial and carcinoma cell lines. Tumor necrosis factor (TNF) stimulated motility in 12 of 14 cell lines in one or more assay systems. The motility-stimulating activity of TNF did not correlate with its antiproliferative activity. In lines whose migration was stimulated by both TNF and %%%scatter%%% %%%factor%%% (SF), a fibroblast-derived cytokine which stimulates epithelial cell motility, saturating concentrations of TNF plus SF induced greater migration than either agent alone. Anti-TNF monoclonal antibody blocked TNF- but not SF-stimulated motility. While various other factors (basic fibroblast growth factor, interleukin 6, interleukin 2, colony-stimulating factor 1) had little or no motility-stimulating activity, phorbol-12-myristate-13-acetate (PMA), a tumor-promoting phorbol ester, scattered and/or stimulated migration in all cell lines studied. Combinations of saturating concentrations of TNF plus PMA or of SF plus PMA induced greater migration than did any agent alone. These findings suggest that (a) carcinoma cell motility may be mediated by multiple biochemical pathways and (b) TNF stimulates epithelial motility by a mechanism different from that of SF and PMA. In vivo, TNF might enhance invasiveness of some carcinomas or stimulate epithelial wound healing.

8/7/46 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

01306591 1999024469
Somatic mutations in the kinase domain of the MET/hepatocyte growth factor
receptor gene in childhood hepatocellular carcinomas
Won Sang Park; Seung Myung Dong; Su Young Kim; Eun Young Na; Min Sun Shin;
Jae Ho Pi; Bum Jun Kim; Jeong Hoon Bae; Young Ki Hong; Kyo Sun Lee; Sug Hyung Lee; Nam Jin Yoo; Ja June Jang; Pack S.; Zhuang Z.; Schmidt L.; Zbar B.; Jung Young Lee
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EMAIL: stingray@cmc.cuk.ac.kr
Journal: Cancer Research, 59/2 (307-310), %%%1999%%%, United States
PUBLICATION DATE: January 15, 1999
CODEN: CNREA
ISSN: 0008-5472
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 20

The MET protooncogene encodes a transmembrane tyrosine kinase identified as
the receptor of a polypeptide known as hepatocyte growth factor/ %%%scatter%%% %%%factor%%%. We performed PCR-based single-strand conformational polymorphism and sequencing analysis of the tyrosine kinase domain of the MET gene (exon 15- 19) in 75 primary liver cancers. Three missense mutations were detected exclusively in 10 childhood hepatocellular carcinomas (HCCs), while no mutations were detected in 16 adult HCCs, 21 cholangiocarcinomas, or 28 hepatoblastomas. The extremely short incubation period from hepatitis B virus %%%infection%%% to the genesis of childhood HCC as compared with the adult HCC suggests that there may be an additional
mechanism that accelerates the carcinogenesis of childhood HCC. Our results
indicate that mutations of the tyrosine kinase domain of the MET gene may he involved in the acceleration of the carcinogenesis in childhood HCC.

8/7/47 (Item 2 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

01257508 1999234958
Interaction of macrophage-stimulating protein with its receptor residues.
Critical for beta chain binding and evidence for independent alpha chain binding
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EMAIL: danilkovitch@mail.ncifcrf.gov
Journal: Journal of Biological Chemistry, 274/42 (29937-29943), %%%1999%%%
, United States
PUBLICATION DATE: October 15, 1999
CODEN: JBCHA
ISSN: 0021-9258
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 36

Macrophage-stimulating protein (MSP) and hepatocyte growth factor/ %%%scatter%%% %%%factor%%% (HGF/SF) are plasminogen-related growth and
motility factors that interact with cell-surface protein tyrosine kinase receptors. Each one is a heterodimeric protein comprising a disulfide-linked alpha chain and a serine protease-like beta chain. Despite structural similarities between MSP and HGF, the primary receptor binding site is located on the chain of HGF/SF but on the beta chain of MSP. To obtain insight into the structural basis for MSP beta chain binding, beta chain structure was modeled from coordinates of an existing model of the HGF beta chain. The model revealed that the region corresponding to the S1 specificity pocket in trypsin is filled by the Asnsup 6sup 8sup 2/Glusup 6sup 4sup 8 interacting pair, leaving a shallow cavity for possible beta chain interaction with the receptor. Mutants in this region were created, and their binding characteristics were determined. A double mutation of Asnsup 6sup 8sup 2/Glusup 6sup 4sup 8 caused diminished binding of the beta
chain to the MSP receptor, and a single mutation of neighboring Argsup 6sup 8sup 3 completely abolished binding. Thus, this region of the molecule is critical for binding. We also found that at equimolar concentrations of free alpha and beta chains, alpha chain binding to receptor was detectable, at levels considerably lower than beta chain binding. The EC$D5inf 0 values determined by quantitative enzyme-linked immunosorbent assay are 0.25 and 16.9 nM for beta and alpha chain, respectively. The data suggest that MSP has two independent binding sites with high and low affinities located in beta and alpha chain, respectively, and that the two sites together mediate receptor dimerization and subsequent activation.

8/7/48 (Item 3 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

01017110 1998263091
Regulation of adhesion and migration in the germinal center microenvironment
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ADDRESS: S.T. Pals, Department of Pathology, Academic Medical Center, University of Amsterdam, Meiberdreef 9, 1105 AZ Amsterdam, Netherlands
Journal: Cell Adhesion and Communication, 6/2-3 (111-116), %%%1998%%%, Netherlands
CODEN: CADCE
ISSN: 1061-5385
DOCUMENT TYPE: Conference Paper

LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 67

T cell dependent humoral immune responses are initiated by the activation of naive B cells in the T cell areas of the secondary lymphoid tissues. This primary B cell activation leads to migration of germinal center (GC) cell precursors into B cell follicles where they engage follicular dendritic cells (FDC) and T cells, and differentiate into memory B cells or plasma cells. Both B cell homing to the GC and interaction with FDC critically depend on integrin-mediated adhesion. We have recently indentified the c-met-encoded receptor tyrosine kinase and its ligand, the growth and motility factor hepatocyte growth factor/%%%scatter%%% %%%factor%%% (HGF/SF), as a novel paracrine signalling pathway regulating B
cell adhesion. The c-Met protein is expressed on B cells localized in the dark zone of the GC (centroblasts) and is induced by CD40 plus BCR ligation. Stimulation of c-Met with HGF/SF, which is produced at high levels by tonsillar stromal cells and FDC, leads to receptor phosphorylation and to enhanced integrin-mediated adhesion of B cells to both VCAM-1 and fibronectin. Interestingly, these responses to HGF/SF are promoted by heparan-sulfate proteoglycan forms of CD44 (CD44-HS). Like c-Met, CD44-HS is induced on B cells by CD40 ligation. It efficiently binds HGF/SF and strongly promotes signalling through c-Met. We conclude that integrin regulation during antigen specific B cell differentiation involves cross-talk between the HGF/SF-c-Met pathway and CD44-HS.

8/7/49 (Item 4 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00756485 97263749
Neoexpression of the c-met/hepatocyte growth factor-%%%scatter%%% %%%factor%%% receptor gene in activated monocytes
Beilmann M.; Odenthal M.; Jung W.; Vande Woude G.F.; Dienes H.- P.; Schirmacher P.
ADDRESS: P. Schirmacher, Institute of Pathology, University Hospital, Langenbeckstr. 1, D-55101 Mainz, Germany
Journal: Blood, 90/11 (4450-4458), %%%1997%%%, United States
PUBLICATION DATE: 19970000
CODEN: BLOOA
ISSN: 0006-4971
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 59

Hepatocyte growth factor-%%%scatter%%% %%%factor%%% (HGF-SF) mediates
mito-, moto-, and morphogenic effects through the MET receptor, a membrane
bound tyrosine kinase. HGF-SF/MET signaling is mitogenic for a large number
of epithelial and endothelial cells and activates organ regeneration. HGF-SF transcripts have been detected in various myeloid cell lines. Therefore, the potential role of HGF-SF/MET signaling for circulating cells of the immune system, especially under conditions of inflammation, was evaluated. Several B- lymphoid and myeloid cell lines were found to express HGF-SF or c-met transcripts, while activity of both genes was mutually exclusive with the exception of low level coexpression in two B-cell lines. HGF-SF transcripts were present in low quantities in freshly isolated peripheral blood mononuclear cells (PBMNCs). In contrast, c-met expression was not detected in freshly isolated cells from peripheral blood, but was induced in monocytes by activation of monocytic or T-cell function. HGF-SF incubation led to an increased c-fos steady state transcript level in myeloblastic K562 cells and moderately promoted cell viability of freshly isolated preactivated monocytes, c-met expression is thus established in activated monocytes, in particular under conditions resembling inflammation, making these cells accessible to functional effects of HGF-SF.

8/7/50 (Item 5 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00436375 96130257
Hepatocyte growth factor: A cytokine mediating endothelial migration in inflammatory arthritis
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Journal: Arthritis and Rheumatism, 39/9 (1566-1575), %%%1996%%%, United
States
PUBLICATION DATE: 19960000
CODEN: ARHEA
ISSN: 0004-3591
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English

Objective. Angiogenesis is an integral component of the vasculoproliferative phase of rheumatoid arthritis (RA). Recently, a heparin- binding cytokine termed hepatocyte growth factor (HGF), or %%%scatter%%% %%%factor%%% (due to its ability to disperse cohesive epithelial colonies), was described. We conducted this study to investigate the hypothesis that this cytokine was present in the milieu of the inflamed joint, and that it contributed to the chemotaxis of endothelial cells in the synovial tissue. Methods. We examined synovial fluid, synovial tissue, and peripheral blood from 91 patients with RA and other arthritides. We used 83 total samples in an enzyme-linked immunosorbent assay to quantitate
the HGF in synovial fluids and peripheral blood. To determine whether the HGF was biologically active, an epithelial %%%scatter%%% %%%factor%%% assay
was performed. Immunohistochemical analysis was used to determine localization in synovial tissues. To define a function for synovial HGF, we preincubated rheumatoid synovial fluids with neutralizing anti-HGF and measured the ability of these synovial fluids to induce endothelial chemotaxis. Results. Synovial fluid from patients with RA contained a mean +/- SEM HGF concentration of 2.0 +/- 0.3 ng/ml, while synovial fluid from patients with other arthritides (including inflammatory arthritis) contained 2.4 +/- 0.7 ng/ml HGF. Osteoarthritis (OA) patient samples contained the smallest quantities of synovial fluid HGF at 0.9 +/- 0.1 ng/ml. RA synovial fluid contained significantly more HGF than did RA peripheral blood (1.1 +/- 0.2 ng/ml) ($P < 0.05$). Rheumatoid synovial fluids induced more scattering of cells than did OA synovial fluids, suggesting a role for this cytokine in rheumatoid joint destruction. Interleukin-1beta induced expression of rheumatoid synovial tissue fibroblast antigenic HGF and %%%scatter%%% %%%factor%%% activity. Immunohistochemically, HGF, as
well as the HGF receptor (the met gene product), localized to significantly more rheumatoid synovial tissue lining cells than normal lining cells ($P < 0.05$). Both HGF and its receptor immunolocalized to subsynovial macrophages
as well. Levels of synovial tissue immunoreactive HGF correlated positively with the number of synovial tissue blood vessels. Anti-HGF neutralized a mean of 24% of the chemotactic activity for endothelial cells found in 10 rheumatoid synovial fluid samples. Conclusion. These results indicate that synovial HGF may contribute to the vasculoproliferative phase of inflammatory arthritides such as RA, by inducing HGF mediated synovial neovascularization. These findings point to a newly described role for HGF in the fibroproliferative phase of RA-associated synovitis.

8/7/51 (Item 6 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00326653 96007374
Restricted expression of the ron gene encoding the macrophage stimulating protein receptor during mouse development
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ADDRESS: R. Breathnach, INSERM U.211, Institut de Biologie-CHR, 9 quai Moncousu, 44035 Nantes Cedex 01, France
Journal: Developmental Dynamics, 204/4 (383-390), %%%1995%%%, United States
PUBLICATION DATE: 19950000
CODEN: DEDYE
ISSN: 1058-8388
DOCUMENT TYPE: Article

LANGUAGES: English SUMMARY LANGUAGES: English

The human ron gene codes for a transmembrane protein tyrosine kinase which
is a receptor for the macrophage stimulating protein. The ron receptor, together with the hepatocyte growth factor/%%%scatter%%% %%%factor%%%
receptor encoded by the proto-oncogene met, and the product of the c-sea proto-oncogene, make up a family of structurally related receptors. We have cloned murine ron cDNA sequences and used them as probes for in situ hybridization and Northern blot experiments. We show that ton gene expression occurs relatively late in development, and is much more restricted than that of the met gene, ron gene expression is detected in specific areas of the central and the peripheric nervous system, as well as in discrete cells in developing bones, and in the glandular epithelia along the digestive tract.

8/7/52 (Item 7 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00296782 95112877
Inhibition of cancer cell motility and invasion by interleukin-12
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ADDRESS: S. Hiscox, Department of Surgery, University Wales College Medicine, Cardiff CF4 4XN, United Kingdom
Journal: Clinical and Experimental Metastasis, 13/5 (396-404), %%%1995%%%, United Kingdom
PUBLICATION DATE: 19950000
CODEN: CEXMD
ISSN: 0262-0898
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English

Tumour cell motility and attachment are crucial requirements in the formation of metastatic lesions. These properties are affected by a number of cytokines including hepatocyte growth factor/%%%scatter%%% %%%factor%%%
(HGF/SF) and several immunoregulatory proteins, including interleukin-12 (IL-12). Although IL-12 has been reported to exhibit potent anti-tumour effects in vivo, a direct effect of IL-12 on cancer cells has not been reported. We show here that IL-12 directly inhibited the attachment of the human colon cancer cell lines HRT18, HT29 and HT115 to Matrigel, HGF/SF-stimulated cell motility and HGF/SF-induced cell invasion through a reconstituted basement membrane. IL-12 did not affect the growth of these
cell lines. Flow cytometry. Western analysis and immunohistochemistry revealed an up-regulation of E-cadherin cell-surface adhesion molecules. These direct effects of IL-12 on colon cancer cells suggest a potentially important role for IL-12 in metastasis.

8/7/53 (Item 8 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00250771 95052782
Association of p120, a tyrosine kinase substrate, with E-cadherin/catenin complexes
Shibamoto S.; Hayakawa M.; Takeuchi K.; Hori T.; Miyazawa K.; Kitamura N.; Johnson K.R.; Wheelock M.J.; Matsuyoshi N.; Takeichi M.; Ito F.
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Journal: Journal of Cell Biology, 128/5 (949-957), %%%1995%%%, United States
PUBLICATION DATE: 19950000
CODEN: JCLBA
ISSN: 0021-9525
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English

p120 was originally identified as a substrate of pp60(src) and several receptor tyrosine kinases, but its function is not known. Recent studies revealed that this protein shows homology to a group of proteins, beta-catenin/Armadillo and plakoglobin (gamma-catenin), which are associated with the cell adhesion molecules cadherins. In this study, we examined whether p120 is associated with E-cadherin using the human carcinoma cell line HT29, as well as other cell lines, which express both of these proteins. When proteins that copurified with E-cadherin were analyzed, not only alpha-catenin, beta-catenin, and plakoglobin but also p120 were detected. Conversely, immunoprecipitates of p120 contained E-cadherin and all the catenins, although a large subpopulation of p120 was not associated with E-cadherin. Analysis of these immunoprecipitates suggests that 20% or less of the extractable E-cadherin is associated with p120. When p120 immunoprecipitation was performed with cell lysates depleted of E-cadherin, beta-catenin was no longer coprecipitated, and the amount of plakoglobin copurified was greatly reduced. This finding suggests that there are various forms of p120 complexes, including p120/E- cadherin/beta-catenin and p120/E-cadherin/plakoglobin complexes; this association profile contrasts with the mutually exclusive association of beta- catenin and plakoglobin with cadherins. When the COOH-terminal catenin binding site was
truncated from E-cadherin, not only beta-catenin but also p120 did not coprecipitate with this mutated E-cadherin. Immunocytological studies showed that p120 colocalized with E-cadherin at cell-cell contact sites, even after non-ionic detergent extraction. Treatment of cells with hepatocyte growth factor/%%%scatter%%% %%%factor%%% altered the level of
tyrosine phosphorylation of p120 as well as of beta-catenin and plakoglobin. These results suggest that p120 associates with E-cadherin at its COOH-terminal region, but the mechanism for this association differs from that for the association of beta- catenin and plakoglobin with E-cadherin, and thus, that p120, whose function could be modulated by growth factors, may play a unique role in regulation of the cadherin-catenin adhesion system.

8/7/54 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

10599812 EMBASE No: 2000065055
Review: Research toward safer resection of the cirrhotic liver
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HPB Surgery (HPB SURG.) (United Kingdom) 1999, 11/5 (285-297)
CODEN: HPBSE ISSN: 0894-8569
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 74

Despite recent advances in hepatic surgery, resection of the cirrhotic liver continues to be fraught with high morbidity and mortality rates. As a result, for many patients requiring resection of HCC the postoperative course is complicated and the probability of cure is diminished by coexisting cirrhosis. In this review, we discuss the characteristics of the cirrhotic liver which make it poorly tolerant of resection and the most common complications that follow such surgery. The main purpose of this paper is to review recent attempts to identify interventions that might be beneficial to cirrhotic patients undergoing resection. These interventions include assessment of liver reserve, advances in surgical technique, and improvement in liver function and regeneration.

8/7/55 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07925446 EMBASE No: 1999398837
Identification and dynamics of a heparin-binding site in hepatocyte growth factor
Zhou H.; Casas-Finet J.R.; Coats R.H.; Kaufman J.D.; Stahl S.J.; Wingfield P.T.; Rubin J.S.; Bottaro D.P.; Byrd R.A.
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Biochemistry (BIOCHEMISTRY) (United States) 09 NOV 1999, 38/45 (14793-14802)

CODEN: BICHA ISSN: 0006-2960
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 46

Hepatocyte growth factor (HGF) is a heparin-binding, multipotent growth factor that transduces a wide range of biological signals, including mitogenesis, motogenesis, and morphogenesis. Heparin or closely related heparan sulfate has profound effects on HGF signaling. A heparin-binding site in the N-terminal (N) domain of HGF was proposed on the basis of the clustering of surface positive charges [Zhou, H., Mazzulla, M. J., Kaufman, J. D., Stahl, S. J., Wingfield, P. T., Rubin, J. S., Bottaro, D. P., and Byrd, R. A. (1998) Structure 6, 109-116]. In the present study, we confirmed this binding site in a heparin titration experiment monitored by nuclear magnetic resonance spectroscopy, and we estimated the apparent dissociation constant (K(d)) of the heparin-protein complex by NMR and fluorescence techniques. The primary heparin- binding site is composed of Lys60, Lys62, and Arg73, with additional contributions from the adjacent Arg76, Lys78, and N-terminal basic residues. The K(d) of binding is in the micromolar range. A heparin disaccharide analogue, sucrose octasulfate, binds with similar affinity to the N domain and to a naturally occurring HGF isoform, NK1, at nearly the same region as in heparin binding. sup 1sup 5N relaxation data indicate structural flexibility on a microsecond-to-millisecond time scale around the primary binding site in the N domain. This flexibility appears to be dramatically reduced by ligand binding. On the basis of the NK1 crystal structure, we propose a model in which heparin binds to the two primary binding sites and the N-terminal regions of the N domains and stabilizes an NK1 dimer.

8/7/56 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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07913295 EMBASE No: 1999386716
Cytokines, for better or worse?
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European Journal of Gastroenterology and Hepatology (EUR. J. GASTROENTEROL. HEPATOL.) (United Kingdom) 1999, 11/9 (957-966)
CODEN: EJGHE ISSN: 0954-691X
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 36

Cytokines play an important role in the pathogenesis of many diseases including liver failure. Both newly described and 'classic' pro-inflammatory cytokines, such as tumour necrosis factor-alpha, have been implicated in both hepatic injury and liver regeneration. In addition, increased circulating concentrations of these cytokines suggest they may have a hormone-like endocrine effect on tissues distant to their production, leading to the hypotension, lung injury and cerebral oedema that occur in such patients. Increased understanding of the cytokine networks involved in acute liver failure may lead to the development of novel therapies, which may reduce the requirement for liver transplantation in this condition.

8/7/57 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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07904570 EMBASE No: 1999378098
Involvement of receptor-type tyrosine kinase gene families in cardiac hypertrophy
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Journal of Hypertension (J. HYPERTENS.) (United Kingdom) 1999, 17/9 (1329-1337)
CODEN: JOHYD ISSN: 0263-6352
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 38

Objective. The activation of protein tyrosine kinases (PTKs) has been postulated to be involved in cell differentiation and proliferation. To elucidate the involvement of tyrosine kinase genes in normal and pathological conditions, we analysed the expression patterns of receptor-type PTKs in the normal and hypertensive hypertrophied heart in rats. Materials and methods. Hypertrophied and normal rat hearts were obtained from hypertensive rats; deoxycorticosterone acetate (DOCA)-salt and 2 kidney-1 clip (2K-1C), and their sham-operated rats, respectively. A reverse transcription-polymerase chain reaction (RT-PCR) was performed using degenerated primers which were designed from highly conserved regions
in the catalytic domains of receptor-type PTKs. The PCR products were ligated into a sequence vector, and subcloned by transforming %%%bacteria%%%. To compare the expression level of these PTK mRNAs in the
normal and hypertrophied heart, we performed semi-competetive RT-PCR and
immunohistochemical and Western blot analyses. Results. Nucleotide sequencing of approximately 80 clones of PTKs revealed 10 receptor-type, five nonreceptor-type and two unknown types in the rat heart. Tie-2/Tek, Ryk, insulin-like growth factor-1 receptor were abundantly expressed in the rat heart as members of receptor-type PTKs. Immunohistochemistry and RT-PCR
demonstrated the presence of platelet-derived growth factor (PDGF)-alpha receptor, PDGF-beta receptor and fibroblast growth factor-3 receptor in both normal and hypertrophied hearts. We also confirmed the presence of Fit-1, KDR/Flk-1,and their ligand vascular endothelial growth factor, c-Met and its ligand hepatocyte growth factor (HGF), and Tie-1, Tie-2/Tek by immunohistochemistry and RT-PCR. The coexpression of cardiac HGF and c-Met
in hypertrophied hearts, especially in 2K-1C rats, was induced more intensively than that in DOCA-salt rats. Conclusion. These findings suggest that HGF/c-Met interactions may play an important role in cardiac hypertrophy and remodeling, probably as a result of the activation of the local renin-angiotensin system.

8/7/58 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2002 Elsevier Science B.V. All rts. reserv.

07893415 EMBASE No: 1999367209
Should Helicobacter pylori %%%infection%%% be taken into account in the management of nonsteroidal anti-inflammatory drug-induced gastroduodenal lesions?
FAUT-IL TENIR COMPTE DE L'%%%INFECTION%%% PAR HELICOBACTER PYLORI AU
COURS DES TRAITEMENTS PAR ANTI-INFLAMMATOIRES NON STEROIDIENS?
Bretagne J.-F.; Pagenault M.; Bourienne A.; Heresbach D.
J.-F. Bretagne, Svc. des Malad. de Appareil Digest., Hopital Pontchaillou, Rennes France
Gastroenterologie Clinique et Biologique (GASTROENTEROL. CLIN. BIOL.) (France) 1999, 23/10 (C48-C64)
CODEN: GCBID ISSN: 0399-8320
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: FRENCH
NUMBER OF REFERENCES: 151

8/7/59 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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07879680 EMBASE No: 1999332191
Hepatoprotective action of adenovirus-transferred HNF-3gamma gene in acute liver injury caused by CClinf 4
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FEBS Letters (FEBS LETT.) (Netherlands) 1999, 459/1 (1-4)
CODEN: FEBLA ISSN: 0014-5793
PUBLISHER ITEM IDENTIFIER: S0014579399012028
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 24

Hepatocyte nuclear factor-3gamma (HNF-3gamma) is an important regulator of liver-specific genes and the expression of this factor is reduced in the liver injured by carbon tetrachloride (CClinf 4). Wistar rats were %%%infected%%% with a recombinant adenovirus carrying the cDNA for HNF-3gamma (AxCAHNF3gamma) via the tail vein and were treated with CClinf 4 by intraperitoneal injection. Liver damage, such as swelling of the hepatocytes and increases in serum marker enzymes were markedly alleviated by AxCAHNF3gamma %%%infection%%%. Interestingly, hepatocyte growth factor (HGF) was strongly induced in the AxCAHNF3gamma-%%%infected%%% liver. Likewise, HNF-1alpha and HNF-1beta levels were increased, but HNF-3alpha and HNF-3beta levels were depressed in the liver. Our results suggest that the transduced HNF-3gamma gene leads to a hepatoprotective effect via the induction of HGF by the combined actions of liver-enriched transcription factors. Copyright (C) 1999 Federation of European Biochemical Societies.

8/7/60 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

07843141 EMBASE No: 1999090609
Analysis of two cosmid clones from chromosome 4 of Drosophila melanogaster reveals two new genes amid an unusual arrangement of repeated sequences
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Genome Research (GENOME RES.) (United States) 1999, 9/2 (137-149)
CODEN: GEREF ISSN: 1088-9051
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 59

Chromosome 4 from Drosophila melanogaster has several unusual features that distinguish it from the other chromosomes. These include a diffuse appearance in salivary gland polytene chromosomes, an absence of recombination, and the variegated expression of P-element transgenes. As part of a larger project to understand these properties, we are assembling a physical map of this chromosome. Here we report the sequence of two cosmids representing ~ 5% of the polytenized region. Both cosmid clones contain numerous repeated DNA sequences, as identified by cross hybridization with labeled genomic DNA, BLAST searches, and dot matrix analysis, which are positioned between and within the transcribed sequences. The repetitive sequences include three copies of the mobile element Hoppel, one copy of the mobile element HE, and 18 DINE repeats. DINE is a novel, short repeated sequence dispersed throughout both cosmid sequences. One cosmid includes the previously described cubitus interruptus (ci) gene and two new genes: that a gene with a predicted amino acid sequence similar to ribosomal protein S3a which is consistent with the Minute(4)101 locus thought to be in the region, and a novel member of the protein family that includes plexin and met-hepatocyte growth factor receptor. The other cosmid contains only the two short 5'-most exons from the zinc-finger-homolog-2 (zfh-2) gene. This is the first extensive sequence analysis of noncoding DNA from chromosome 4. The distribution of the various repeats suggests its organization is similar to the beta-heterochromatic regions near the base of the major chromosome arms. Such a pattern may account for the diffuse banding of the polytene chromosome 4 and the variegation of many P-element transgenes on the chromosome.

8/7/61 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE

07817545 EMBASE No: 1999289951
Effects of deletion-type human hepatocyte growth factor on murine septic model
Kondo H.; Tani T.; Kodama M.
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Journal of Surgical Research (J. SURG. RES.) (United States) 1999, 85/1 (88-95)
CODEN: JSGRA ISSN: 0022-4804
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 29

Background. %%%Sepsis%%% is known to be the main cause of multiple organ failure. The liver especially is vulnerable to the stress of %%%infection%%%. In this study, the effects of deletion-type human hepatocyte growth factor (dHGF) on a murine septic model were studied. Materials and methods. %%%Sepsis%%% was induced in male adult Sprague-Dawley rats by cecal ligation and puncture method (CLP). Controls were given a sham operation. Intravenous injection of 1000 mug/kg dHGF or the same volume of vehicle was given every 12 h for 3 days before and/or after the CLP from a central vein catheter inserted 1 week prior to the operation. The daily percentage of survival after CLP was followed up for 1 week, and blood samples and liver specimens were collected from the surviving animals 72 h after CLP or sham operation. Results. The survival rate, the degree of liver damage and liver protein synthesis, and coagulation function were all favorable in the dHGF-treated animals compared to the untreated animals. Immunohistochemical staining showed that dHGF prevented the disappearance of thrombomodulin (TM) in liver sinusoid endothelium. Conclusions. dHGF appears to prevent liver injury caused by disturbance of microcirculation through preservation of TM expression and the antithrombotic function in the endothelium of sinusoids. dHGF also facilitates repair of damaged hepatic tissue by stimulating regeneration of the cells and by preserving hepatic functions such as protein synthesis. dHGF exerts protective effects on even quiescent hepatocytes, but is most effective on injured but competent hepatocytes.

8/7/62 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE

07744750 EMBASE No: 1999227000
Hepatocyte growth factor prevents endotoxin-induced lethal hepatic failure in mice
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Hepatology (HEPATOLOGY) (United States) 1999, 30/1 (151-159)
CODEN: HPTLD ISSN: 0270-9139
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 54

%%%Sepsis%%% and endotoxemia are involved in the development of fulminant hepatic failure, the prognosis of which is extremely poor and the mortality is high, with no available effective therapy. Here, we report that hepatocyte growth factor (HGF) exerts potent antiapoptotic effects in vivo and effectively prevents endotoxin-induced fulminant hepatic failure in mice. The animals were intraperitoneally injected three times with 120 mug human recombinant HGF or saline 6 hours and 30 minutes before and 3 hours after an intraperitoneal injection of lipopolysaccharide (LPS) and D-galactosamine (GAlN). Administration of LPS + GalN, without HGF, rapidly led to massive hepatocyte apoptosis and severe liver injury, and all mice died of hepatic failure within 8 hours. In contrast, administration of human recombinant HGF strongly suppressed extensive progress of hepatocyte apoptosis and the liver injury induced by LPS + GAlN, and 75% of the

HGF-treated mice survived. Moreover, HGF strongly induced Bcl-xL
expression
and blocked apoptotic signal transduction upstream of CPP32 (caspase-3) in the liver, thereby leading to inhibition of massive hepatocyte apoptosis. We suggest that HGF may well have the potential to prevent fulminant hepatic failure, at least through its potent antiapoptotic action.

8/7/63 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE

07684538 EMBASE No: 1999156309
Hyperplasia of gastric mucosa in donor rats orally %%%infected%%% with Taenia taeniaeformis eggs and in recipient rats surgically implanted with the larvae in the abdominal cavity
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Parasitology Research (PARASITOL. RES.) (Germany) 1999, 85/6
(431-436)
CODEN: PARRE ISSN: 0044-3255
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 14

Rats heavily %%%infected%%% with Taenia taeniaeformis larvae in the
liver
show a remarkable increase in their stomach weight, hyperplasia, and hypergastrinemia. However, it is unknown what causes these phenomena. Hence, as a preliminary study to investigate the importance of larval parasitism in the liver, two experiments were done. In the first experiment, 14 donor rats were orally inoculated with 3,000 T. taeniaeformis eggs. In the second experiment, 136-300 of the larvae obtained from the rats were surgically implanted into the abdominal cavity of 7 recipient rats. Gastrin levels and histopathological changes in the gastric mucosa were investigated. In all, 11 donor rats showed hypergastrinemia and hyperplasia, 5 recipient rats showed gastric mucosal hyperplasia accompanied by excessive mucous cell proliferation, and 2 recipient rats showed hypergastrinemia. These results suggest that parasitism of the liver by the larvae is not essential for the development of hyperplasia and that factors from the larvae might cause these phenomena.

8/7/64 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE

07588044 EMBASE No: 1999067355
%%%Infection%%% and immunity mediated by the carbohydrate
recognition
domain of the Entamoeba histolytica Gal/GalNAc lectin
Dodson J.M.; Lenkowski P.W. Jr.; Eubanks A.C.; Jackson T.F.G.H.; Napodano J.; Lyerly D.M.; Lockhart L.A.; Mann B.J.; Petri W.A. Jr.
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Journal of Infectious Diseases (J. INFECT. DIS.) (United States) 1999
, 179/2 (460-466)
CODEN: JIDIA ISSN: 0022-1899
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 38

Entamoeba histolytica causes invasive amebiasis, a major parasitic disease of the developing world, whose primary symptoms are liver abscess and colitis. All strains of E. histolytica express a 260-kDa surface Gal/GalNAc lectin that is antigenically conserved and immunogenic. The lectin is required for adherence to human intestinal epithelial cells and contact- dependent killing of immune effector cells. By expression cloning, the carbohydrate recognition domain (CRD) was identified within the lectin heavy- subunit cysteine-rich region. Of interest for a hepatic parasite, the CRD had sequence identity to the receptor-binding domain of
hepatocyte
growth factor (HGF) and competed with HGF for binding to the c-Met HGF receptor. In an animal model of invasive disease, immunization with the CRD inhibited liver- abscess formation, yet in humans, a naturally acquired immune response against the CRD did not persist.

8/7/65 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE

07554363 EMBASE No: 1999039103
An anchor for activation
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Nature (NATURE) (United Kingdom) 14 JAN 1999, 397/6715 (109-111)
CODEN: NATUA ISSN: 0028-0836
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 10

8/7/66 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE

07541090 EMBASE No: 1999031582
Augmentation of water-immersion stress-induced gastric mucosal lesions in BALB/c mice %%%infected%%% with Helicobacter felis
Matsushimaa Y.; Kinoshita Y.; Watanabe M.; Hassan S.; Fukui H.; Maekawa T.; Okada A.; Kawanami C.; Kishi K.; Watanabe N.; Nakao M.; Chiba T.
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Digestion (DIGESTION) (Switzerland) 1999, 60/1 (34-40)
CODEN: DIGEB ISSN: 0012-2823
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 23

Background and Aims: Inoculation of Helicobacter felis into the murine stomach has been reported to induce chronic gastric inflammation and may
be
a model of Helicobacter pylori-induced chronic gastritis. In this study, to characterize H. felis-induced gastritis, the gastric production of interleukin-1beta (IL-1beta) and hepatocyte growth factor (HGF) was measured in mice. Methods: Gastric mucosal lesions were induced in H. felis-%%%infected%%% BALB/c mice by water-immersion stress. The
severity
score of gastric erosions per stomach was measured as the sum of the
length
of erosions. Gene expression of IL-1beta and HGF were analyzed by
Northern
blot analysis and production of HGF was examined using the enzyme immunoassay method. Results: Water-immersion stress induced gastric
mucosal
lesions accompanied by increased expression of IL-1beta mRNA. H. felis %%%infection%%% evoked enhanced expression of IL-1beta and HGF genes.
When
H. felis-%%%infected%%% mice were stressed by water immersion, the
mucosal
lesions were more severe than those in non-%%%infected%%% mice.
Moreover,
IL-1beta gene expression as well as HGF production was further increased. Conclusions: Although H. felis inoculation did not cause gastric mucosal erosions by itself, it augmented the stress-induced erosions.

8/7/67 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE

07522808 EMBASE No: 1999003474
Amphotropic retroviral vectors displaying hepatocyte growth factor-envelope fusion proteins improve transduction efficiency of primary hepatocytes

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Human Gene Therapy (HUM. GENE THER.) (United States) 20 NOV 1998, 9/17
(2469-2479)
CODEN: HGTHE ISSN: 1043-0342
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 33

The development of retroviral vectors with cell-specific targeting capabilities will be an important step toward successful in vitro gene therapy. This article describes the generation of a retroviral vector with enhanced binding abilities for cells bearing the c-Met receptor: the Madin-Darby canine kidney (MDCK) cell line and primary hepatocytes. The human hepatocyte growth factor (HGF) was displayed on murine amphotropic retroviral vectors by fusion to the viral transmembrane envelope glycoprotein (TM). The resulting chimeric envelope HGF-TM was expressed in
an amphotropic packaging cell line producing viral particles that display both HGF-TM and the wild-type envelope. These modified viral particles had a titer equivalent to that of unmodified particles. Modified particles %%%infected%%% MDCK cells more efficiently than did unmodified amphotropic
retrovirus. Adding anti-HGF antibodies to the viral vector particle supernatant prior to %%%infection%%% confirmed that the increased %%%infection%%% was mediated by the HGF moiety. The chimeric viruses also
%%%infected%%% primary mouse and nonhuman primate fetal hepatocytes more
effectively. Furthermore, these cells could be induced to proliferate by the modified HGF-TM viruses. Since exogenous HGF is primarily taken up by the liver, these results may have implications for retroviral vector design for liver-directed human gene therapy.

8/7/68 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE

07439701 EMBASE No: 1998352801
Regulation of hepatic cytochrome P450 2C11 by transforming growth factor-beta, hepatocyte growth factor, and interleukin-11
Iber H.; Morgan E.T.
Dr. E.T. Morgan, Department of Pharmacology, Emory University, Atlanta, GA 30322 United States
Drug Metabolism and Disposition (DRUG METAB. DISPOS.) (United States)
1998, 26/10 (1042-1044)
CODEN: DMDSA ISSN: 0090-9556
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 20

Injection of rats with %%%bacterial%%% lipopolysaccharide down-regulates
P450 (P450) 2C11 (2C11) mRNA to about 20% of its control levels after only 6 hr, and this level is maintained for at least 48 hr. Although we and others have demonstrated that this effect may be at least partially mediated by the cytokines interleukin-1, interleukin-6, and tumor necrosis factor-alpha, as well as by glucocorticoids, the time courses and potencies of 2C11 repression by each single mediator suggested that no cytokine alone is responsible for the entire time course of 2C11 suppression during inflammation. Here, we show that transforming growth factor-beta, hepatocyte growth factor, and interleukin-11 are potent inhibitors of 2C11 expression. In all three cases, 0.1 ng/ml was enough to down-regulate 2C11 mRNA levels to 50% of control. Interleukin-8, a cytokine that is secreted during the acute phase response but does not influence the liver acute phase response, did not affect 2C11 expression. The various mediators have different time courses of 2C11 down- regulation, indicating that the roles of each may be different at different phases of the response.

8/7/69 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE

07392538 EMBASE No: 1998307942
Effects of keratinocyte and hepatocyte growth factor in vivo: Implications for retrovirus-mediated gene transfer to liver
Bosch A.; McCray P.B. Jr.; Walters K.S.; Bodner M.; Jolly D.J.; Van Es H.H.G.; Nakamura T.; Matsumoto K.; Davidson B.L.
Dr. B.L. Davidson, Department of Internal Medicine, 200 EMRB, University of Iowa, Iowa City, IA 52242 United States
Human Gene Therapy (HUM. GENE THER.) (United States) 10 AUG 1998, 9/12
(1747-1754)
CODEN: HGTHE ISSN: 1043-0342
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 30

We have previously shown that intravenous administration of keratinocyte growth factor (KGF) induces hepatocyte proliferation, allowing for efficient and noninvasive in vivo gene transfer with high-titer retroviral vectors in mice. The distinctive periportal distribution of transduced cells led us to investigate the ability of virus-sized particles to perfuse the liver adequately after growth factor treatment. We found that perfusion
was adequate, and that transduction was limited to the periportal region because only those cells were stimulated to divide. Cells in this region also showed increased expression of Ram-1, the receptor for the murine Moloney leukemia virus (MoMLV) amphotropic envelope, after KGF treatment.
In further studies we found that recombinant hepatocyte growth factor (HGF)
induces a different population of hepatocytes to divide and upregulate Ram-1. The differential pattern of induction suggested that combining KGF and HGF would improve gene transfer efficiency further. Indeed, simultaneous delivery of both growth factors leads to an overall increase in the number of proliferating cells. Importantly, when coupled with MoMLV delivery, efficiency of gene transfer increased. These results confirm the utility of growth factors for noninvasive hepatic gene transfer in mice, and demonstrate how experiments to define the mechanism of transduction can
be taken advantage of to develop improved gene transfer protocols.

8/7/70 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE

07365924 EMBASE No: 1998223718
Expression of growth control and differentiation genes in human lens epithelial cells with extended life span
Fleming T.P.; Song Z.; Andley U.P.
U.P. Andley, Dept. of Ophthalmology/Visual Sci., Washington Univ. School of Medicine, 660 S. Euclid Avenue, St. Louis, MO 63110 United States
Investigative Ophthalmology and Visual Science (INVEST. OPHTHALMOL. VIS.
SCI.) (United States) 1998, 39/8 (1387-1398)
CODEN: IOVSD ISSN: 0146-0404
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 55

PURPOSE. Peptide growth factors including hepatocyte growth factor (HFG),
platelet-derived growth factor (PDGF), and epidermal growth factor (EGF) are mitogens for many cell types and may act as regulators of lens epithelial cell growth and differentiation. The present study was undertaken to investigate the expression of growth factor receptors and crystallin genes in the human lens epithelial cell line HLE B-3, created by %%%infection%%% with Adenol 12-simian virus 40 (Ad12-SV40) hybrid virus.
METHODS. Reverse transcriptase-polymerase chain reaction (RT-PCR) with gene
specific primers was used to detect transcripts, and Southern and western blot analyses were used for identification of gene products. Functional analysis of PDGF receptor was performed by measuring the effect of PDGF-BB

on Casup 2sup + release, cell growth, and western blot analysis, by using an antiphosphotyrosine antibody. RESULTS. Human lens epithelial B-3 cells expressed the growth factor receptors HGF-R, EGF-R, and PDGF-Rbeta, but not
PDGF-Ralpha, and also expressed the oncogenes H-ras and raf and the growth
inhibitor transforming growth factor-betainf 1. Stimulation of PDGF-Rbeta with PDGF-BB in HLE B-3 cells increased phosphorylation of the receptor, was associated with an increase in intracellular Casup 2sup + levels, and produced a small increase in cell growth. In addition, HLE B-3 cells expressed transcripts for alphaA-, betaB2-crystallins, and expressed the corresponding proteins. The transcripts for alphaA-crystallin decreased markedly at higher passages. CONCLUSIONS. The above findings suggest that
the increased growth potential of human lens epithelial cells by Ad12-SV40 %%%infection%%% maintained certain lens-specific properties and response to
PDGF.

8/7/71 (Item 18 from file: 73)
DIALOG(R)File 73:EMBASE

07355635 EMBASE No: 1998219861
Susceptibility of epithelial cells to Pseudomonas aeruginosa invasion and cytotoxicity is upregulated by hepatocyte growth factor
Fleiszig S.M.J.; Vallas V.; Jun C.H.; Mok L.; Balkovetz D.F.; Roth M.G.; Mostov K.E.
S.M.J. Fleiszig, School of Optometry, University of California, Berkeley, CA 94720-2020 United States
AUTHOR EMAIL: fleiszig@socrates.berkeley.edu
Infection and Immunity (INFECT. IMMUN.) (United States) 1998, 66/7 (3443-3446)
CODEN: INFIB ISSN: 0019-9567
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 26

Normal cell polarity protects epithelial cells against Pseudomonas aeruginosa invasion and cytotoxicity. Using epithelial cell clones with selective defects in sorting of membrane constituents, and using hepatocyte growth factor pretreatment, we found that polarized susceptibility to P. aeruginosa can be altered without disrupting tight junctions. The results also showed that cellular susceptibility factors for invasion and cytotoxicity are not the same, although both are localized to the basolateral cell surface in polarized epithelial cells.

8/7/72 (Item 19 from file: 73)
DIALOG(R)File 73:EMBASE

07297802 EMBASE No: 1998191039
Ribavirin inhibits protein synthesis and cell proliferation induced by mitogenic factors in primary human and rat hepatocytes
Ilyin G.P.; Langouet S.; Rissel M.; Delcros J.-G.; Guillouzo A.; Guguen-Guillouzo C.
Dr. G.P. Ilyin, INSERM U49, Unite de Recherches Hepatologiques, Hopital Pontchaillou, 35033 Rennes France
Hepatology (HEPATOLOGY) (United States) 1998, 27/6 (1687-1694)
CODEN: HPTLD ISSN: 0270-9139
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 35

Ribavirin, a guanosine analog, used in combination with interferon alpha (IFN-alpha) in the treatment of chronic hepatitis induced by hepatitis C virus (HCV) %%%infection%%%, has been shown to improve liver histology and
to decrease transaminases even when administered alone. We analyzed the direct effects of ribavirin on the liver by using primary cultures of human and rat hepatocytes. Between 10 to 60 mumol/L, ribavirin was found to inhibit both the synthesis and secretion of whole proteins in a time- and dose-dependent fashion. Such an effect was confirmed by the measurement of
albumin and haptoglobin secretion rates. [sup 3H]-Thymidine incorporation was suppressed both in hepatocyte growth factor-stimulated human hepatocytes and in epidermal growth factor (EGF)-stimulated rat hepatocytes
in the presence of ribavirin. The inhibitory effect on DNA synthesis was associated with a delayed progression to S phase of the cell cycle, as determined by flow cytometry and detection of cyclin A and cdc2 which are two proteins expressed during the S phase. The inhibition of DNA synthesis, caused by 50 mumol/L ribavirin, was completely restored by the addition of 80 mumol/L guanosine. These observations demonstrate that ribavirin at concentrations close to those found in plasma of treated patients can directly affect hepatic functions in vitro. Its effects could, however, be reduced in vivo by guanosine salvage supply.

8/7/73 (Item 20 from file: 73)
DIALOG(R)File 73:EMBASE

07263317 EMBASE No: 1998163150
Relations between %%%scatter%%% %%%factor%%%, quality index and attenuation for x- ray beams
Bjarngardt B.E.; Vadash P.
B.E. Bjarngardt, Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA 19104 United States
Physics in Medicine and Biology (PHYS. MED. BIOL.) (United Kingdom) 1998, 43/5 (1325-1330)
CODEN: PHMBA ISSN: 0031-9155
PUBLISHER ITEM IDENTIFIER: S0031915598860600
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 10

The relations between the attenuation factor, the normalized phantom %%%scatter%%% %%%factor%%% and the quality index are examined using a
semiempirical formula for the dose on the central axis of an x-ray beam in water. The study is restricted to depths and field sizes sufficient for electron equilibrium. The results are compared with data in the recent literature. It is concluded that for x-ray beams in the energy range 4-25 MV the normalized %%%scatter%%% %%%factors%%% can be calculated from the
dose-weighted average linear attenuation coefficient in water, determined from transmission measurements in a narrow- beam geometry or from the quality index.

8/7/74 (Item 21 from file: 73)
DIALOG(R)File 73:EMBASE

07240684 EMBASE No: 1998139536
Hepatocyte growth factor protects the liver against hepatitis C virus in patients on regular hemodialysis
Rampino T.; Libetta C.; Mazzone A.; Gregorini M.; Soccio G.; Ranghino A.; Maggio M.; Guallini P.; Girola S.; Dal Canton A.
T. Rampino, Dipartimento Medicina Interna, Policlinico San Matteo, 27100 Pavia Italy
Journal of Chemotherapy (J. CHEMOTHER.) (Italy) 1998, 10/2 (164-166)
CODEN: JCHEE ISSN: 1120-009X
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 4

8/7/75 (Item 22 from file: 73)
DIALOG(R)File 73:EMBASE

07231395 EMBASE No: 1998091098
The Ras/Rac1/Cdc42/SEK/JNK/c-Jun cascade is a key pathway by which agonists stimulate DNA synthesis in primary cultures of rat hepatocytes
Auer K.L.; Contessa J.; Brenz-Verca S.; Pirola L.; Rusconi S.; Cooper G.; Abo A.; Wymann M.P.; Davis R.J.; Birrer M.; Dent P.
P. Dent, Department of Radiation Oncology, Box 980058, Massey Cancer Center, 401 College Street, Richmond, VA 23298-0058 United States

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Molecular Biology of the Cell (MOL. BIOL. CELL) (United States) 1998, 9/3 (561-573)
CODEN: MBCEE ISSN: 1059-1524
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 53

The ability of signaling via the JNK (c-Jun NHinf 2-terminal kinase)/stress-activated protein kinase cascade to stimulate or inhibit DNA synthesis in primary cultures of adult rat hepatocytes was examined. Treatment of hepatocytes with media containing hyperosmotic glucose (75 mM
final), tumor necrosis factor alpha (TNFalpha, 1 ng/ml final), and hepatocyte growth factor (HGF, 1 ng/ml final) caused activation of JNK1. Glucose, TNFalpha, or HGF treatments increased phosphorylation of c-Jun at
serine 63 in the transactivation domain and stimulated hepatocyte DNA synthesis. %%%Infection%%% of hepatocytes with poly-L-lysine-coated adenoviruses coupled to constructs to express either dominant negatives Ras(N17), Rac1(N17), Cdc42(N17), SEK1sup -, or JNK1sup - blunted the abilities of glucose, TNFalpha, or HGF to increase JNK1 activity, to increase phosphorylation of c-Jun at serine 63, and to stimulate DNA synthesis. Furthermore, %%%infection%%% of hepatocytes by a recombinant
adenovirus expressing a dominant-negative c-Jun mutant (TAM67) also blunted
the abilities of glucose, TNFalpha, and HGF to stimulate DNA synthesis. These data demonstrate that multiple agonists stimulate DNA synthesis in primary cultures of hepatocytes via a Ras/Rac1/Cdc42/SEK/JNK/c-JUn pathway.
Glucose and HGF treatments reduced glycogen synthase kinase 3 (GSK3) activity and increased c-Jun DNA binding. Co-%%%infection%%% of hepatocytes
with recombinant adenoviruses to express dominant- negative forms of PIinf 3 kinase (p110alpha/p110chi) increased basal GSK3 activity, blocked the abilities of glucose and HGF treatments to inhibit GSK3 activity, and reduced basal c-Jun DNA binding. However, expression of dominant-negative PIinf 3 kinase (p110alpha/p110chi) neither significantly blunted the abilities of glucose and HGF treatments to increase c-Jun DNA binding, nor inhibited the ability of these agonists to stimulate DNA synthesis. These data suggest that signaling by the JNK/stress-activated protein kinase cascade, rather than by the PIinf 3 kinase cascade, plays the pivotal role in the ability of agonists to stimulate DNA synthesis in primary cultures of rat hepatocytes.

8/7/76 (Item 23 from file: 73)
DIALOG(R)File 73:EMBASE

07222599 EMBASE No: 1998090779
Biological effects of targeted inactivation of hepatocyte growth factor-like protein in mice
Bezerra J.A.; Carrick T.L.; Degen J.L.; Witte D.; Degen S.J.F.
J.A. Bezerra, Div. of Gastroenterology/Nutrition, Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229 United States
AUTHOR EMAIL: jorge.bezerra@chmcc.org
Journal of Clinical Investigation (J. CLIN. INVEST.) (United States) 01 MAR 1998, 101/5 (1175-1183)
CODEN: JCINA ISSN: 0021-9738
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Hepatocyte growth factor-like protein (HGFL) is a liver-derived serum glycoprotein involved in cell proliferation and differentiation, and is proposed to have a fundamental role in embryogenesis, fertility, hematopoiesis, macrophage activation, and tissue repair. To assess the in vivo effects of total loss of HGFL, we generated mice with targeted disruption of the gene resulting in loss of the protein. Disruption of the HGFL gene allowed for normal embryogenesis, and followed a Mendelian pattern of genetic transmission. Mice homozygous for the targeted allele (HGFL(-/-) mice) are fertile, and grow to adulthood without obvious phenotypic abnormalities in unchallenged animals, except for development of lipid- containing cytoplasmic vacuoles in hepatocytes throughout the liver lobules. These histologic changes are not accompanied by discernible changes in synthetic or excretory hepatic functions. Hematopoiesis appears unaltered, and although macrophage activation is delayed in the absence of HGFL, migration to the peritoneal cavity upon challenge with thioglycollate was similar in HGFL(-/-) and wild-type mice. Challenged with incision to skin, HGFL(-/-) mice display normal would healing. These data demonstrate that HGFL is not essential for embryogenesis, fertility, or wound healing. HGFL- deficient mice will provide a valuable means to assess the role of HGFL in hepatic and systemic responses to inflammatory and
%%%infectious%%%
stimuli in vivo.

8/7/77 (Item 24 from file: 73)
DIALOG(R)File 73:EMBASE

07107693 EMBASE No: 1997358524
Fetal rat hepatocytes: Isolation, characterization, and transplantation in the nagase analbuminemic rats
Lilja H.; Arkadopoulos N.; Blanc P.; Eguchi S.; Middleton Y.; Meurling S. ; Demetriou A.A.; Rozga J.
Dr. J. Rozga, Liver Support Research Laboratory, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Augeles, CA 90048 United States
Transplantation (TRANSPLANTATION) (United States) 1997, 64/9 (1240-1248)
CODEN: TRPLA ISSN: 0041-1337
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 46

Background. In contrast to adult hepatocytes, fetal hepatocytes (FH) are thought to be highly proliferative, less immunogenic, and resistant to cryopreservation and ischemic injury. These qualities could enhance FH engraftment, proliferation, and gene transfer requiring active DNA synthesis. Methods. Rat FH were obtained using the nonperfusion collagenase/DNase digestion method. Free and cultured cells were studied using electron microscopy, fluorescence-activated cell sorting, and Northern analysis using alpha-fetoprotein and albumin as markers of hepatocyte lineage. DNA synthetic activity was measured in quiescent and mitogen-stimulated fetal and adult hepatocytes by (sup 3H)thymidine incorporation. Susceptibility of cultured FH to retrovirally mediated gene transfer was studied using an amphotropic retroviral vector carrying the Escherichia coli lac-Z gene. Nagase analbuminemic rats were used as recipients to study the effects of intraportal FH transplantation. Analysis of serum albumin was carried out by enzyme-linked immunosorbent assay. Results. In fetal liver, 87+/-2% of the cells showed morphological and molecular features of hepatocytes. DNA synthetic activity in nonstimulated cultured FH was 10 times greater than the maximal hepatocyte growth factor-driven response in adult rat hepatocytes. A total of 5-15% FH stained positive for X-gal; results of transduction in adult hepatocyte cultures were negative. In Nagase analbuminemic rat recipients, FH produced
significant amounts of albumin only when a hepatic regenerative stimulus was applied. Immunohistochemistry confirmed presence of albumin-positive hepatocytes. Conclusions. Fetal rat liver from the late gestation period is highly enriched with hepatocyte progenitors. They are highly proliferative and susceptible to retroviral transduction and can engraft and function in the adult rat liver if transplanted under a hepatic regenerative stimulus.

8/7/78 (Item 25 from file: 73)
DIALOG(R)File 73:EMBASE

07100848 EMBASE No: 1997382712
Surgical treatment for severe acute pancreatitis: Factors which affect the surgical results
Yamamoto M.; Takeyama Y.; Ueda T.; Hori Y.; Nishikawa J.; Saitoh Y.
M. Yamamoto, The First Department of Surgery, Kobe University School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe City 650 Japan
Hepato-Gastroenterology (HEPATO-GASTROENTEROLOGY) (Germany) 1997,
44/18 (1560-1564)
CODEN: HEGAD ISSN: 0172-6390
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 22

Surgical treatment for severe acute pancreatitis has not yet yielded satisfactory results. Several factors which might affect the surgical results of severe acute pancreatitis were analyzed in this study. The presence or absence of %%%infection%%% was not important as a factor determining the surgical results. The severity scores and some biochemical parameters such as CRP, IL-6, PMN-E, HGF seemed to be closely related to surgical results. It was likely that a significant decrease in lymphocyte counts in the blood on admission was closely related to the prognosis of the surgical patients. Timing and procedures for surgery should be more seriously considered in the treatment for patients with such poor general conditions.

8/7/79 (Item 26 from file: 73)
DIALOG(R)File 73:EMBASE

07098877 EMBASE No: 1997380741
Cytokines and the liver
Simpson K.J.; Lukacs N.W.; Colletti L.; Strieter R.M.; Kunkel S.L.
K.J. Simpson, Ctr. for Liver/Digestive Disorders, Royal Infirmary, Edinburgh EH3 9YW United Kingdom
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Journal of Hepatology (J. HEPATOL.) (Denmark) 1997, 27/6 (1120-1132)
CODEN: JOHEE ISSN: 0168-8278
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 131

8/7/80 (Item 27 from file: 73)
DIALOG(R)File 73:EMBASE

07024220 EMBASE No: 1997078284
Dimerization of Fab fragments enables ready screening of phage antibodies that affect hepatocyte growth factor/%%%scatter%%% %%%factor%%% activity on
target cells
Zaccolo M.; Griffiths A.P.; Prospero T.D.; Winter G.; Gherardi E.
M. Zaccolo, Imperial Cancer Research Fund Lab., MRC Centre, Hills Road, Cambridge CB2 2QH United Kingdom
European Journal of Immunology (EUR. J. IMMUNOL.) (Germany) 1997, 27/3
(618-623)
CODEN: EJIMA ISSN: 0014-2980
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 44

A number of applications of antibodies in diagnosis and therapy require multivalent reagents either because of the polymeric nature of the antigens or because biological activity depends on an effect on the formation of homodimeric species. Here, we report a procedure for mass screening of phage-derived monomeric antibody fragments that depend on valency for activity. As a model system, a set of 13 phage-derived human Fab fragments were first selected against mouse and human recombinant hepatocyte growth
factor/%%%scatter%%% %%%factor%%% (HGF/SF), a high molecular weight
polypeptide growth factor related to the blood protease plasminogen and involved in development and cancer. These Fab fragments were subsequently screened for an effect on HGF/SF activity either as monomeric fragments or
after dimerization with a monoclonal antibody (9E10) directed against a peptide tag on the fragments. Fab were identified that either inhibited or enhanced HGF/SF activity on target cell lines, but dimerization was required for this effect. The approach proposed should facilitate mass screening of phage-derived antibody fragments that depend on multiple valency for activity.

8/7/81 (Item 28 from file: 73)
DIALOG(R)File 73:EMBASE

06947538 EMBASE No: 1997232055
Mitogen-stimulated lymphocyte transformation and hepatocyte growth factor
in alcoholic cirrhosis patients
Antoljak N.; Topic E.; Duvnjak M.; Kastelan M.; Vrkic N.; Zuntar I.
Dr. N. Antoljak, Clinical Institute of Chemistry, School of Medicine, Sestre milosrdnice University Hosp., Vinogradska c. 29, 10000 Zagreb Croatia
Acta Clinica Croatica (ACTA CLIN. CROAT.) (Croatia) 1997, 36/2-3
(63-70)
CODEN: ACLCE ISSN: 0353-9466
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH;
SERBOCROATIAN
NUMBER OF REFERENCES: 23

Impaired immunodefense and %%%infections%%% are very common and often
fatal complications in liver alcoholic cirrhosis patients. Results of the studies on circulating lymphocyte ability to undergo blast transformation with polyclonal mitogens in vitro are different. On the other side, the hepatocyte growth factor (HGF) is a multifunctional cytokine, the most potent mitogen for hepatocytes, but also for multipotent hemopoietic cells. HGF levels usually increase during liver regeneration. The aim of the study was to determine whether the ability of blast transformation and HGF levels change in liver cirrhosis. Blast transformation of lymphocytes was measured with polyclonal mitogens and HGF levels by the ELISA method in 33 patients with alcoholic cirrhosis and in a group of 42 healthy volunteers. Blast transformation of lymphocytes with PHA, ConA and PWM was diminished in 72.7%, 78.8%, and 66.7% of patients, respectively. In healthy volunteers, blast transformation was within the normal range. HGF levels were higher in cirrhotics than in healthy volunteers (0.98+/-0.38 vs. 0.2+/-0.06 ng/ml, $p<0.001$). These preliminary results suggested that alcohol consumption reduced the ability of blast stimulation, at the same time increasing the HGF levels. Further studies of the relationship between HGF and in vitro blast transformation of lymphocytes in liver cirrhosis are required.

8/7/82 (Item 29 from file: 73)
DIALOG(R)File 73:EMBASE

06827812 EMBASE No: 1997110311
Lack of specificity of albumin-mRNA-positive cells as a marker of circulating hepatoma cells
Muller C.; Petermann D.; Pfeffel F.; Oesterreicher C.; Fugger R.
Dr. C. Muller, KAGH, UIM IV, Wahringer Gurtel 18-20, A-1090 Vienna Austria
Hepatology (HEPATOLOGY) (United States) 1997, 25/4 (896-899)
CODEN: HPTLD ISSN: 0270-9139
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 17

The aim of the study was to assess the specificity of albumin-messenger RNA (mRNA)-positive cells in peripheral blood as an indicator for circulating malignant hepatocytes. Albumin-mRNA-positive cells in the peripheral blood mononuclear cell (PMNC) fraction were detected by reverse-transcription polymerase chain reaction (RT-PCR).
Albumin-mRNA-positive cells in PMNC were found in 12 of 19 (63%) patients with hepatocellular carcinoma, but also in 22 of 25 (88%) patients with chronic hepatitis without evidence for hepatoma, and in 18 of 19 (94%) of patients with acute viral hepatitis. In addition, 8 of 28 (28%) of healthy control individuals had also albumin-mRNA-positive cells in peripheral blood. PMNC known to be spontaneously negative for albumin-mRNA could be induced in vitro to transcribe albumin-mRNA after activation with a variety of substances such as interleukin-1 (IL-1) plus concanavalin A (Con A), IL-2, %%%bacterial%%% lipopolysaccharide, platelet derived growth factor, alpha-fibroblast growth factor, or hepatocyte growth factor. These results show that the majority of patients with acute and chronic liver disease without evidence for hepatocellular carcinoma has albumin-mRNA- positive cells in their PMNC fraction indicating the nonspecificity of that parameter for the presence of circulating malignant hepatooytes. In addition, in vitro experiments suggest that PMNC are capable of

transcribing mRNA for albumin at a low level after activation. In vivo-activated PMNC are likely to be the source of positivity in healthy controls, patients with nonmalignant acute and chronic liver disease, and patients with hepatocellular carcinoma.

8/7/83 (Item 30 from file: 73)
DIALOG(R)File 73:EMBASE

06802560 EMBASE No: 1997085045
Hepatocyte growth factor/%%%scatter%%% %%%factor%%% promotes adhesion of
lymphoma cells to extracellular matrix molecules via alphainf 4betainf 1 and alpha$D5/betainf 1 integrins
Weimar I.S.; De Jong D.; Muller E.J.; Nakamura T.; Van Gorp Gijsbert J.M.H.H.; De Gast C.; Gerritsen W.R.
Dr. W.R. Gerritsen, Dept. of Immunology/Medical Oncology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam Netherlands
Blood (BLOOD) (United States) 1997, 89/3 (990-1000)
CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 76

Hepatocyte growth factor (HGF)/%%%scatter%%% %%%factor%%% (SF) is the
ligand for a tyrosine kinase cell surface receptor encoded by the MET protooncogene (c- MET). HGF/SF can induce proliferation and motility in epithelial cells and promotes invasion of carcinoma cells and NIH3T3 fibroblasts transfected with both HGF/SF and c-MET genes. Our results show
that HGF/SF and c-MET also play a role in adhesion and invasion of human lymphoma cells. c-MET mRNA is expressed in hemopoietic cells, such as hemopoietic progenitor cells (CD34sup + cells) in bone marrow (BM) and mobilized peripheral blood, immature B cells in cord blood and BM, and germinal center B-centroblasts. In normal peripheral blood B cells, which are c-METsup -, c-MET expression was induced by PMA, ConA, HGF/SF, and Epstein-Barr virus (EBV) %%%infection%%%. Using immunohistochemistry, we
detected c-MET on the cell surface of large activated centroblasts in lymph nodes from patients with B-non-Hodgkin's lymphoma and Hodgkin's disease. In
the latter group, c-MET expression correlated well with the presence of EBV. Because HGF/SF and c-MET promote metastasis of carcinoma cells, we studied the effects of c-MET stimulation by HGF/SF of B-lymphoma cells on properties relevant for metastasis, ie, adhesion, migration, and invasion. HGF/SF stimulated adhesion of the c-METsup + B-cell lines to the extracellular matrix molecules fibronectin (FN) and collagen (CN) in a dose dependent manner. However, adhesion to laminin was not affected by HGF/SF.
Adhesion to FN was mediated by betainf 1-integrins alphainf 4betainf 1 (VLA4) and alpha$D5beta (VLA5) since blocking antibodies against betainf 1-
(CD29), alphainf 4(CD49d), or alpha$D5- (CD49e) integrin subunits, completely reversed the effect of HGF/SF. Furthermore, HGF/SF induced adhesion was abrogated by addition of genistein, which blocks protein tyrosine kinases, including c- MET. Addition of HGF/SF resulted in a sixfold increase in migration of c-MET B-lymphoma cells through Matrigel, compared to medium alone. In rat fibroblast cultures, HGF/SF doubled the number of c-METsup + B-lymphoma cells that invaded the fibroblast monolayer. In these adhesion, migration and invasion assays HGF/SF had no effect on c-MET cell lines. In conclusion, c- MET is expressed or can be induced on immature, activated, and certain malignant B cells. HGF/SF increased adhesion of c-METsup + B-lymphoma cells to FN and CN, mediated via betainf 1-integrins alphainf 4betainf 1 and alpha$D5betainf 1, and furthermore promoted migration and invasion.

8/7/84 (Item 31 from file: 73)
DIALOG(R)File 73:EMBASE

06770623 EMBASE No: 1997052116
Hepatocyte growth factor in assessment of acute pancreatitis: Comparison with C-reactive protein and interleukin-6
Ueda T.; Takeyama Y.; Hori Y.; Nishikawa J.; Yamamoto M.; Saitoh Y.
Y. Takeyama, First Department of Surgery, Kobe University School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650 Japan
Journal of Gastroenterology (J. GASTROENTEROL.) (Japan) 1997, 32/1 (63-70)
CODEN: JOGAE ISSN: 0944-1174
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 32

Serum levels of hepatocyte growth factor (HGF), C-reactive protein (CRP), and interleukin-6 (IL-6) were determined at the time of admission in 38 patients with acute pancreatitis. The clinical utility of HGF for the detection of severe pancreatitis and for predicting prognosis, %%%bacterial%%% %%%infection%%% (%%%infected%%% pancreatic necrosis or
%%%sepsis%%%), and organ dysfunction (liver, kidney, and lung) during the clinical course of acute pancreatitis was compared with the clinical utility of CRP and IL-6 by analysis of receiver operator characteristic (ROC) curves. The optimum cutoff levels of HGF for severity, prognosis, %%%infection%%%, hepatic dysfunction, renal dysfunction, and respiratory dysfunction were 0.9, 1.1, 1.0, 1.1, 1.1, and 1.0 ng/ml, respectively. HGF was as useful as CRP and more useful than IL-6 for detection of severe pancreatitis and for predicting hepatic dysfunction. Moreover, HGF was more
useful than CRP or IL-6 for predicting prognosis, renal dysfunction, and respiratory dysfunction. However, for predicting %%%infection%%%, CRP was
more useful than HGF. These results suggest that serum HGF levels on admission may be a useful new clinical parameter for determining the prognosis of acute pancreatitis and that HGF may be closely related to the organ dysfunction of acute pancreatitis.

8/7/85 (Item 32 from file: 73)
DIALOG(R)File 73:EMBASE

06752284 EMBASE No: 1997033763
Cytokines and Helicobacter pylori - A growth area
Playford R.
R. Playford, Univ. Division of Gastroenterology, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW United Kingdom
Gut (GUT) (United Kingdom) 1996, 39/6 (881-882)
CODEN: GUTTA ISSN: 0017-5749
DOCUMENT TYPE: Journal; Note
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 10

8/7/86 (Item 33 from file: 73)
DIALOG(R)File 73:EMBASE

06752267 EMBASE No: 1997033746
Increased production of interleukin 1beta and hepatocyte growth factor may contribute to foveolar hyperplasia in enlarged fold gastritis
Yasunaga Y.; Shinomura Y.; Kanayama S.; Higashimoto Y.; Yabu M.; Miyaaki Y.; Kondo S.; Murayama Y.; Nishibayashi H.; Kitamura S.; Matsuzawa Y.
Dr. Y. Yasunaga, Second Dept. of Internal Medicine, Osaka University, Medical School, 2-2 Yamadaoka, Suita, Osaka 565 Japan
Gut (GUT) (United Kingdom) 1996, 39/6 (787-794)
CODEN: GUTTA ISSN: 0017-5749
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 42

Background and Aims. It has been reported that eradication of Helicobacter pylori improves fold width in H. pylori associated enlarged fold gastritis. The aim of this study was to clarify the mechanism of fold thickening in this condition. Patients and Methods. In eight patients with enlarged fold gastritis and 13 patients without enlarged folds, the presence of H. pylori %%%infection%%%, inflammatory infiltrates, mucosal plasia, and epithelial cell proliferation in the body mucosa were investigated, and production of transforming growth factor alpha (TGFalpha), hepatocyte growth factor (HGF), and interleukin 1beta (IL

1beta) was determined by a competitive reverse transcription/polymerase chain reaction method and in vitro short-term culture of biopsy specimens. Results. In the patients with enlarged fold gastritis, inflammatory infiltrates including macrophages increased with H. pylori colonisation in the body. Foveolar thickness and proliferating cell nuclear antigen (PCNA) labelling index were increased. Messenger RNA levels of HGF, but not TGFalpha, were increased, and release of HGF and IL 1beta was increased. HGF release, which was positively correlated with IL 1beta release and foveolar thickness, decreased in the presence of IL 1 receptor antagonist. After eradication of H. pylori, inflammatory infiltrates, IL 1beta and HGF release decreased with concomitant decreases in PCNA labelling index, foveolar thickness and fold width. Conclusions. Increased IL 1beta and HGF production caused by H. pylori %%%infection%%% may contribute to fold thickening of the stomach by stimulating epithelial cell proliferation and foveolar hyperplasia in patients with enlarged fold gastritis.

8/7/87 (Item 34 from file: 73)
DIALOG(R)File 73:EMBASE

06733083 EMBASE No: 1997014553
Fibroblast growth factor 2 and the protease activity of tumor
Maier J.A.M.; Mariotti M.; Meneghini L.; Cavallaro U.; Wu Z.; Massazza G.; Campioni D.; Corallini a.; Barbanti-Brodano G.; Soria M.R.
J.A.M. Maier, Dept. Biomed. Sciences/Technologies, HSR, University of Milano, 58 Via Olgettina, 20132 Milano Italy
AUTHOR EMAIL: <maierj@dibit.hsr.it>
Fibrinolysis (FIBRINOLYSIS) (United Kingdom) 1996, 10/5-6 (309-315)
CODEN: FBRIE ISSN: 0268-9499
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 34

In BK virus (BKV)/tat transgenic mice, the relatively low incidence and long latency period of tumors indicate that the BKV/tat transgene is not sufficient for the expression of a complete oncogenic phenotype. Since angiogenesis and the production of proteases are critical for tumor growth, we evaluated the expression of two potent angiogenic molecules, fibroblast growth factor type 2 (FGF-2), and hepatocyte growth factor (HGF), and of the fibrinolytic system in cell lines isolated from tumors of different histotypes developed by BKV/tat transgenic mice. Here we show that the overexpression of HGF is a unique feature of spindle cells derived from murine Kaposi's sarcoma-like lesions, whereas FGF-2 is detectable in all the cell lines tested. Interestingly, FGF-2 is secreted only by adenocarcinoma-derived T53 cells that show a fully transformed phenotype in
vitro. In addition, T53 cells synthesize larger amounts of urokinase-type plasminogen activator (uPA) than the other cell lines studied. This is due to the secretion of FGF-2 and not to the presence of extracellular Tat. We conclude that the high levels of expression of uPA and its receptor, and the very low levels of plasminogen activator inhibitor type 1, may contribute to the tumorigenic phenotype of T53 cells.

8/7/88 (Item 35 from file: 73)
DIALOG(R)File 73:EMBASE

06657264 EMBASE No: 1996322140
Production of IL-1alpha and IL-1beta by human skin equivalents parasitized by Sarcoptes scabiei
Arlian L.G.; Vyszenski-Moher D.L.; Rapp C.M.; Hull B.E.
Department of Biological Sciences, Wright State University,Dayton, OH 45435 United States
Journal of Parasitology (J. PARASITOL.) (United States) 1996, 82/5 (719-723)
CODEN: JOPAA ISSN: 0022-3395
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Human skin equivalents (HSEs) were used as a model to investigate interleukin (IL)-1alpha and IL-1beta secretions by keratinocytes stimulated by Sarcoptes scabiei (SS). SS mites burrowed into the stratum corneum when
placed on the surface of cultured HSEs. Mites lived for 14 days. Mites and mite products induced cells in the HSEs to secrete IL-1alpha and IL-1beta within 16 hr. Scabies mites induced production of greater amounts of IL-1alpha than IL- 1beta. Hepatocyte growth factor in the culture medium at
3 and 30 ng/ml upregulated the secretions of both IL-1alpha and IL-1beta by
mite-infested skin equivalents, whereas 10 ng/ml of IL-6 upregulated production of only IL-1beta. Therefore, these cytokines were important immunomodulating factors influencing keratinocyte secretion of IL-1alpha and IL-1beta in vitro. The results of this study provide the first evidence that keratinocytes (possibly fibroblasts) in the skin produce these cytokines in response to scabies mites or other ectoparasitic arthropods. Because IL-1alpha and IL-1beta are potent inducers of inflammation and keratinocytes are among the first effector cells to encounter scabies mites and their products, these cells may be key initiators of the inflammatory/immune reaction to scabies.

8/7/89 (Item 36 from file: 73)
DIALOG(R)File 73:EMBASE

06633807 EMBASE No: 1996298618
Effects of hepatocellular mitogens on cytokine-induced nitric oxide synthesis in human hepatocytes
Liu Z.-Z.; Cui S.; Billiar T.R.; Dorko K.; Halfter W.; Geller D.A.; Michalopoulos G.; Beger H.-G.; Albina J.; Nussler A.K.
Department General Surgery, University of Ulm, Park Street,D-89073 Ulm

Germany
Journal of Leukocyte Biology (J. LEUKOCYTE BIOL.) (United States) 1996
, 60/3 (382-388)
CODEN: JLBIE ISSN: 0741-5400
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The synthesis of induced nitric oxide (NO) is regulated by several cytokines, including growth factors produced following hepatic injury and inflammation. However, little information is available on the role of growth factors in regulating the inducible NO synthase in human hepatocytes. The capacity of hepatocellular mitogens (HGF, EGF, and TGF-alpha) to regulate the inducible NO synthase (iNOS) was studied in human hepatocytes incubated with inflammatory cytokines and lipopolysaccharide (LPS). Furthermore, the effects of hepatic mitogens on NO-induced changes in DNA and protein synthesis was studied. It was found that NO-mediated decrease of protein and DNA synthesis were partially reversed by the mitogens. This was associated with a downregulation in cytokine-mediated hepatocyte NO formation, iNOS mRNA expression, and NOS
enzyme activity. Cytokine-induced NO formation or SNAP, an NO donor, added
with cytokines increased hepatocyte chromatin condensation but no DNA fragmentation was observed. The increase in chromatin condensation was partially reversed by hepatic mitogens and corresponded with the inhibition of NO production. Thus, the hepatic mitogens, HGF, EGF, and TGF-alpha, all suppress iNOS expression and it is the suppression of iNOS that appears to be responsible for the mitogen-reduced preservation of DNA and protein synthesis and prevention of chromatin condensation.

8/7/90 (Item 37 from file: 73)
DIALOG(R)File 73:EMBASE

06619624 EMBASE No: 1996284403
Spindle cells isolated from Kaposi's sarcoma-like lesions of BKV/tat-transgenic mice co-express markers of different cell types
Cavallaro U.; Gasparini C.; Soria M.R.; Maier J.A.M.
Dept. Biological Technological Res., San Raffaele Scientific Institute, Via Olgettina 58,I-20132 Milano Italy
AIDS (AIDS) (United Kingdom) 1996, 10/11 (1211-1219)
CODEN: AIDSE ISSN: 0269-9370
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Objective: To characterize murine spindle cells isolated from Kaposi's sarcoma-like skin lesions developed in BK virus (BKV)/tat-transgenic mice. Methods: Kaposi's sarcoma-like spindle cells isolated from the lesions were propagated in vitro, and their phenotype was investigated using a panel of antibodies against various cell markers and angiogenic factors. Immunofluorescence and Western blot techniques were used. Results: We observed co-expression of antigens specific for endothelial, smooth muscle and antigen-presenting cells, suggesting that cells from the TTB cell line represent poorly differentiated vascular precursors. Since TTB cells were derived from highly vascularized skin lesions, it is noteworthy that they synthesize a complex mixture of angiogenic factors, including fibroblast growth factor-2, vascular endothelial growth factor, placental growth factor, and hepatocyte growth factor. Due to their role in invasiveness and angiogenesis, we also observed the expression of urokinase plasminogen activator (uPA), uPA receptor, and plasminogen activator inhibitor-type 1 by TTB cells. Conclusions: Our results suggest that TTB cells share several features with human Kaposi's sarcoma spindle cells and can be a useful in vitro system to study the molecular mechanisms involved in Kaposi's sarcoma pathogenesis. Moreover, they synthesize a complex mixture of angiogenic factors and are growth-inhibited by the anti-angiogenic drug AGM-1470.

8/7/91 (Item 38 from file: 73)
DIALOG(R)File 73:EMBASE

06578148 EMBASE No: 1996242721
Clinical significance of serum levels of human hepatocyte growth factor in patients with acute viral hepatitis
Naito Y.; Niiya M.; Fujise K.; Kawamura T.; Watanabe R.
Japanese Journal of Gastroenterology (JPN. J. GASTROENT.) (Japan) 1996
, 93/7 (455-461)
CODEN: NIPAA ISSN: 0446-6586
DOCUMENT TYPE: Journal; Article
LANGUAGE: JAPANESE SUMMARY LANGUAGE: ENGLISH; JAPANESE

We studied the relationship of serum levels of human hepatocyte growth factor (hHGF) to causative viruses and clinical features in 63 patients at our hospital with serologically diagnosed acute viral hepatitis. Serum levels of hHGF were not correlated with the type of hepatitis virus (A, B, and C) during the acute phase (p<0.60) but were correlated with results of the hepaplastin test (p<0.01). Furthermore, the difference in serum levels of hHGF between severe (levels on hepaplastin test<40%) and nonsevere cases
of hepatitis was significant (p<0.001), and serum levels of hHGF became normal as levels of alanine aminotransferase decreased. However, serum levels of hHGF in prolonged cases of hepatitis (time until normalization of alanine aminotransferase 13 weeks) tended to be slightly lower than in nonprolonged cases (p<0.47). These results suggest that serum levels of hHGF are useful to determine the prognoses of patients with severe hepatitis and to estimate the time until liver damage heals.

8/7/92 (Item 39 from file: 73)
DIALOG(R)File 73:EMBASE

06553917 EMBASE No: 1996214555
Gastric mucosal hepatocyte growth factor in Helicobacter pylori gastritis and peptic ulcer disease
Taha A.S.; Curry G.W.; Morton R.; Park R.H.R.; Beattie A.D.
Department of Gastroenterology, Eastbourne General Hospital, King's Drive,Eastbourne BN21 2UD United Kingdom
American Journal of Gastroenterology (AM. J. GASTROENTEROL.) (United
States) 1996, 91/7 (1407-1409)
CODEN: AJGAA ISSN: 0002-9270
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Objectives: Hepatocyte growth factor (HGF) is increasingly recognized for its role in a variety of hepatic and systemic diseases. Its relationship to gastritis has not been studied. We aimed at measuring gastric mucosal HGF levels in the presence or absence of Helicobacter pylori gastritis, in peptic ulcers, and in response to H. pylori eradication. Methods: Fifty one patients were studied. Patients were not entered if they had liver disease, malignancy, or any systemic illness. HGF was measured in gastric antral incubates using an enzyme-linked immunosorbent assay. Assessments were repeated 6 wk after a 2-wk course of anti-H. pylori triple therapy in 12 patients. Code numbers were used for blinding. Results: The median gastric mucosal HGF level was 36 ng/gm/tissue in patients with H. pylori gastritis (n = 33) compared with 19 ng/gm in 18 negative controls (p = 0.0024), 18 ng/gm after the eradication of H. pylori (p = 0.021), 23 ng/gm in all patients with ulcers (n = 10), and 26 ng/gm/tissue in H. pylori-positive ulcers (n = 7). Conclusions: Gastric mucosal HGF levels were elevated in H. pylori gastritis and reduced by its eradication. These results are relevant to our understanding of the increased gastric cell proliferation in patients with H. pylori-related gastritis.

8/7/93 (Item 40 from file: 73)
DIALOG(R)File 73:EMBASE

06535064 EMBASE No: 1996198957
Hepatocyte growth factor expressed by a retrovirus-producing cell line enhances retroviral transduction of primary hepatocytes: Implications for in vivo gene transfer
Pages J.-C.; Loux N.; Bellusci S.; Farge D.; Bennoun M.; Vons C.; Jouanneau J.; Franco D.; Briand P.; Weber A.
INSERM U380, ICGM, 22 rue Mechain,75014 Paris France
Biochemical and Biophysical Research Communications (BIOCHEM. BIOPHYS.
RES. COMMUN.) (United States) 1996, 222/3 (726-731)
CODEN: BBRCA ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Hepatocyte Growth Factor (HGF) is the more potent mitogen of mature hepatocytes. We have examined the effect of human HGF expression by a recombinant retroviral cell line (MFG-LacZ) on retroviral transduction of primary mouse and human hepatocytes. The HGF in the supernatant of MFG-LacZ
cell line was correctly processed and biologically active. Transduction of mouse and human hepatocytes with the supernatant of transfected cells was increased 5-fold, as determined by beta-galactosidase activity. The production of HGF was stable and did not interfere with the viral titers of the producer cells. This study provides evidence that expression of HGF within a retrovirus-producer cell line increases the transduction rate of primary hepatocytes. Since the number of corrected cells is a limiting step for phenotypic correction of liver deficiencies, our approach should improve hepatic gene therapy efficiency. Furthermore this cell line should be useful for in vivo liver gene therapy.

8/7/94 (Item 41 from file: 73)
DIALOG(R)File 73:EMBASE

06513508 EMBASE No: 1996177362
14th Meeting of the Digestive Epithelial Cell Study group
XIV^E REUNION DU CLUB D'ETUDE DES CELLULES EPITHELIALES
DIGESTIVES (C.E.C.E.D.)
Eto B.; Boisset M.; Desjeux J.-F.; Souli A.; Presset O.; Tsocas A.; Chariot J.; Roze C.
Laboratoire de Biologie CNAM,75003 Paris France
Gastroenterologie Clinique et Biologique (GASTROENTEROL. CLIN. BIOL.) (
France) 1996, 20/4 (379-393)
CODEN: GCBID ISSN: 0399-8320
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: FRENCH

8/7/95 (Item 42 from file: 73)
DIALOG(R)File 73:EMBASE

06492189 EMBASE No: 1996148179
Hepatocyte proliferation and serum hepatocyte growth factor levels in

patients with alcoholic hepatitis
Hillan K.J.; Logan M.C.; Ferrier R.K.; Bird G.L.A.; Bennett G.L.; McKay I.C.; MacSween R.N.M.
Genentech Inc, 460 Point San Bruno Boulevard,South San Francisco, CA 94080 United States
Journal of Hepatology (J. HEPATOL.) (Denmark) 1996, 24/4 (385-390)
CODEN: JOHEE ISSN: 0168-8278
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Background/Methods: Hepatocyte growth factor is thought to be important
in stimulating growth of the liver following injury. In this study we have measured serum levels of hepatocyte growth factor together with hepatocyte
proliferation in liver biopsies, by detection of the Ki-67 antigen, in 23 patients with alcoholic hepatitis. Results: Serum hepatocyte growth factor was elevated in all patients (median 0.9 ng/ml; range 0.6-7.7 ng/ml; normal <0.5 ng/ml) and there was a positive correlation between hepatocyte growth factor levels and hepatocyte proliferation in the biopsies. Conclusions: These results demonstrate that in acute alcoholic hepatitis the liver proliferates in response to injury and suggest that hepatocyte growth factor may be one of the growth factors responsible for this proliferative activity.

8/7/96 (Item 43 from file: 73)
DIALOG(R)File 73:EMBASE

06379644 EMBASE No: 1996044717
Isolation of Xenopus HGF gene promoter and its functional analysis in embryos and animal caps
Nakamura H.; Tashiro K.; Shiokawa K.
Laboratory of Molecular Embryology, Zoological Institute, Fac Science, University of Tokyo, 7-3-1 Hongo,Tokyo 113 Japan
Roux's Archives of Developmental Biology (ROUX'S ARCH. DEVELOP. BIOL.)
(Germany) 1996, 205/5-6 (300-310)
CODEN: WRABD ISSN: 0930-035X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Previously, we isolated Xenopus HGF (hepatocyte growth factor) cDNA and showed in Xenopus embryos that expression of this gene starts at the late gastrula stage mainly in the ventral mesoderm, and furthermore that the expression is induced in animal cap by activin A and bFGF (basic fibroblast growth factor). Here we have cloned the Xenopus HGF gene, covering a 14 kb 5'-upstream region and a 0.2 kb 5'-coding region. Within about 0.5 kb of the 5'-flanking region, the Xenopus HGF gene contained a TATA-like element
AATGAAA, one putative NF-1 binding site, two NF-IL-6 binding motif sequences, one putative TGF-beta-dependent inhibitory element (TIE) and one
AP-1 binding site. A recombinant circular plasmid consisting of a 1.7 kb HGF promoter region and the %%%bacterial%%% chloramphenicol acetyltransferase (CAT) gene was first expressed at the late gastrula stage in the ventral mesoderm, as was the endogenous HGF gene. The expression of
the fusion gene was induced in animal cap cells by activin A and bFGF although induction by the latter was not so strong. Using a series of 5'-deletion constructs introduced into animal caps, silencer elements, which seem to be essential for the gene's regionally correct expression, and the element responsible for induction by activin were found. The results show that the HGF gene promoter isolated here contains elements which may endow the gene with the regulative function for its temporally and spatially regulated expression, although the element necessary for induction by bFGF seems to be missing.

8/7/97 (Item 44 from file: 73)
DIALOG(R)File 73:EMBASE

06352741 EMBASE No: 1996003780
Evaluation of hepatocyte growth-promoting factors in treating 1687 cases of fulminant hepatitis
Zhang Y.; Kong X.; Zheng G.; Chen G.; Yang E.
Research Inst. for Liver Disease, Guangzhou Hospital of Air Force,Guangzhou 510602 China
Chinese Medical Journal (CHIN. MED. J.) (China) 1995, 108/12 (928-929)
CODEN: CMDJA ISSN: 0366-6999
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH

8/7/98 (Item 45 from file: 73)
DIALOG(R)File 73:EMBASE

06345921 EMBASE No: 1996002326
Significant elevation of serum human hepatocyte growth factor levels in patients with acute pancreatitis
Ueda T.; Takeyama Y.; Toyokawa A.; Kishida S.; Yamamoto M.; Saitoh Y.
First Department of Surgery, Kobe University School of Medicine, 7-5-2 Kusunoki-cho,Chuo-ku, Kobe 650 Japan
Pancreas (PANCREAS) (United States) 1996, 12/1 (76-83)
CODEN: PANCE ISSN: 0885-3177
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Serum levels of human hepatocyte growth factor (HGF) were determined in 38 patients with acute pancreatitis by an enzyme-linked immunosorbent assay. The mean value of serum HGF levels on admission in the 38 patients was 1.69 +/- 0.40 (SEM) ng/ml. In 35 patients, serum HGF levels were found to be positive (>0.39 ng/ml), with an incidence of 92.1%. In 17 patients, they were >1.0 ng/ml, which was the cutoff value for fulminant hepatic failure. Serum HGF levels in the patients with severe acute pancreatitis (2.30 +/- 0.61 ng/ml; mean +/- SEM) were significantly higher than those in the patients with mild and moderate acute pancreatitis (0.63 +/- 0.06 ng/ml). Sixteen of seventeen patients whose serum HGF levels were >1.0 ng/ml were evaluated as severe acute pancreatitis. Serum HGF levels were significantly elevated in the patients with higher Ranson scores, higher APACHE II scores, or higher computed tomography grades. Serum HGF levels in
the patients with organ dysfunction (liver, kidney, or lung) were significantly higher than those in the patients without organ dysfunction. Moreover, serum HGF levels on admission in the nonsurvivors (3.17 +/- 1.30 ng/ml) were significantly higher than those in the survivors (1.22 +/- 0.33 ng/ml). The mortality rate of the patients showing serum HGF levels >2.0 ng/ml on admission was 50%. In the patients with a lethal outcome, the mean serum HGF level remained constantly >2.50 ng/ml during hospitalization. The serum HGF level reflected the clinical course of the disease rapidly and distinctly. Serum HGF levels increased with complications such as organ failure, %%%infected%%% pancreatic necrosis, and %%%sepsis%%% and decreased
with successful intensive and surgical treatments. These results suggest that serum human HGF levels may reflect the severity, organ dysfunction, and prognosis in acute pancreatitis.

8/7/99 (Item 46 from file: 73)
DIALOG(R)File 73:EMBASE

06328980 EMBASE No: 1995364350
Role of %%%scatter%%% %%%factor%%% and the c-met protooncogene in the
pathogenesis of AIDS-associated Kaposi's sarcoma
Polverini P.J.; Nickoloff B.J.
Laboratory of Molecular Pathology, Department of Oral Medicine, Michigan Univ. School of Dentistry,Ann Arbor, MI 48109-1078 United States
Advances in Cancer Research (ADV. CANCER RES.) (United States) 1995, 66/- (235-253)
CODEN: ACRSA ISSN: 0065-230X
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Kaposi's sarcoma is a highly lethal tumor in patients with sexually acquired AIDS. A number of etiologic agents have been implicated in the development of this disease in this patient population and there is ample evidence that aberrant production of and responsiveness to KS tumor and

host cell-derived cytokines plays a central role in the pathogenesis of AIDS-KS. In this review we propose that aberrant expression SF and c-met
is
central to the pathogenesis of KS. KS is a serious and life-threatening consequence for many patients with AIDS. Unfortunately, current
therapeutic
strategies for the treatment of this complex neoplasm have met with only limited success. In view of the poor survival rates for AIDS-KS patients which continue to decline at an alarming rate, it is eminently clear that a better understanding of the etiology and pathogenesis of this form of KS is needed if novel therapeutic strategies designed to successfully combat this disease are to be developed. If our hypothesis is validated, one could envision several approaches whereby the modulation of SF/c-met function or production might lead to a reduction in the incidence and severity of KS lesions. Antibody therapy directed against either SF-producing tumor cells or against the c-met receptor might decrease the incidence of new tumors
by
limiting their clonal expansion and lead to regression of established tumors by blocking SF-mediated tumor cell proliferation and neovascularization. It might also be possible to suppress production of SF or accessory cytokines involved in the induction SF production and thus short circuit SF/c-met growth-promoting effects. We have outlined a novel hypothesis for understanding the mechanism underlying the development of AIDS-associated KS. This is most certainly not the whole story, however. Clearly, other cytokines and alterations in natural host defenses and the immune system contribute significantly to the development of AIDS-associated KS. We believe, however, that recognition of SF/c-met as
a
participant in this disease is necessary if we are to more fully understand the pathogenesis of AIDS-associated KS.

8/7/100 (Item 47 from file: 73)
DIALOG(R)File 73:EMBASE

06202179 EMBASE No: 1995239436
Translocation of activated Rho from the cytoplasm to membrane ruffling area, cell-cell adhesion sites and cleavage furrows
Takaishi K.; Sasaki T.; Kameyama T.; Tsukita S.; Tsukita S.; Takai Y.
Dept. Molecular Biology Biochemistry, Osaka University Medical School,Suita 565 Japan
Oncogene (ONCOGENE) (United Kingdom) 1995, 11/1 (39-48)
CODEN: ONCNE ISSN: 0950-9232
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Rho small GTP-binding protein regulates various cell functions, such as formation of stress fibers and, focal adhesions, cell motility, membrane ruffling, cytokinesis and smooth muscle contraction in mammalian cells and bud formation in the yeast Saccharomyces cerevisiae. As to the functioning sites of Rho in Saccharomyces cerevisiae, we have recently shown that
RHO1
protein, a homologue of mammalian RhoA, is concentrated to the growth region of the cells where cortical actin patches are clustered. However, in mammalian cells, the functioning sites of Rho have not yet been studied. In the present study, MDCK cell lines stably expressing myc-tagged RhoA (myc-RhoA) were prepared and localization of myc-RhoA was first immunohistochemically examined using an anti-myc antibody. In the resting cells, almost all of myc-RhoA was observed in the cytosol. When the cells were stimulated with phorbol ester or hepatocyte growth factor, membrane rufflings were induced and myc-RhoA was translocated to the membrane ruffling area. Moreover, myc-RhoA was translocated from the cytosol to the cell-cell adhesion sites when the cells were transferred from a low to normal Casup 2sup + medium. RhoA was also concentrated to the cleavage furrows during cytokinesis in Swiss 3T3 cells. Translocation of myc-RhoA to the membrane ruffling area was inhibited by prior microinjection into the cells of Rho GDI, a negative regulator of Rho which inhibits activation of Rho, or of C3, an exoenzyme of Clostridium botulinum which ADP-ribosylates Rho and inhibits its functions, indicating that both activation and functioning of Rho are essential for the translocation of Rho. The ERM (Ezrin, Radixin, Moesin) family members were colocalized with RhoA at all of these sites. However, RhoA was not apparently observed at the focal adhesion plaque where vinculin was localized. These results suggest that at least one of the functioning sites of Rho is the ERM family-controlled actin filament/plasma membrane association sites.

8/7/101 (Item 48 from file: 73)
DIALOG(R)File 73:EMBASE

06197446 EMBASE No: 1995234948
Helicobacter pylori increases gene expression of hepatocyte growth factor in human gastric mucosa
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Biochemical and Biophysical Research Communications (BIOCHEM. BIOPHYS.
RES. COMMUN.) (United States) 1995, 210/3 (960-965)
CODEN: BBRCA ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Helicobacter pylori (H. pylori) induces hyperproliferation of the gastric mucosa. This study was designed to clarify whether H. pylori %%%infection%%% is involved in the gene expression of hepatocyte growth factor (HGF), a potent stimulator of cell proliferation in gastric mucosa. Levels of HGF mRNA were determined by a reverse
transcription-polymerase
chain reaction in endoscopic gastric biopsy specimens from 9 control subjects and 9 patients with H. pylori %%%infection%%%. In patients with
H.
pylori %%%Infection%%%, levels of HGF mRNA in gastric mucosa were significantly higher than those in control subjects. HGF mRNA levels in patients with H. pylori %%%infection%%% were correlated with the severity of gastric mucosal inflammation. Our observations indicate that H. pylori %%%infection%%% increases the expression of HGF gene in gastric mucosa probably through the mucosal inflammation.

8/7/102 (Item 49 from file: 73)
DIALOG(R)File 73:EMBASE

05933989 EMBASE No: 1994341948
Hepatotrophic activity in mouse serum %%%infected%%% with
plerocercoids
of Spirometra erinacei
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Parasitology Research (PARASITOL. RES.) (Germany) 1994, 80/8
(629-633)
CODEN: PARRE ISSN: 0044-3255
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

To investigate the mechanism by which liver weigth increases during pleroceroid %%%infections%%% as well as the possible existence of a hepatocyte-growth-factor (HGF)-like substance in the serum of mice %%%infected%%% with Spirometra erinacei plerocercoids, liver DNA
synthesis
was measured in vive and in vitro. %%%Infection%%% with S. erinacci plerocercoids significantly stimulated DNA synthesis in mouse parenchymal hepatocytes prior to the increase in liver weight, at least partly by stimulating the induction of the salvage pathways of pyrimidine biosynthesis. Furthermore, %%%infected%%% mouse serum directly
stimulated
DNA synthesis in cultured mouse parenchymal hepatocytes. These results suggest that an HGF-like substance is present in the serum of mice %%%infected%%% with S. erinacei plerocercoids.

8/7/103 (Item 50 from file: 73)
DIALOG(R)File 73:EMBASE

05837654 EMBASE No: 1994245305
Roles of growth factors and of tumor necrosis factor-alpha on liver cell proliferation induced in rats by lead nitrate

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Laboratory Investigation (LAB. INVEST.) (United States) 1994, 71/1 (35-41)
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BACKGROUND: A single intravenous injection of lead nitrate to rats induces a synchronized wave of hepatocyte proliferation without accompanying liver cell necrosis. However, the mechanism of the mitogenic effect of lead nitrate is not known, and whether hepatocyte growth factor (HGF), transforming growth factor-alpha (TGF-alpha), and transforming growth factor-beta1 (TGF-beta1) play any role in it have not been investigated. These growth factors have indeed been shown to provide either
positive or negative stimuli for liver cell regeneration after partial hepatectomy or liver cell necrosis. Moreover, there are reports showing that administration of non-necrogenic doses of tumor necrosis factor-alpha (TNF-alpha) to rats lead to an enhanced proliferation of hepatocytes and liver nonparenchymal cells. Lead is known to sensitize animals to lethal effects of %%%bacterial%%% lipopolysaccharides (LPS), suggesting that lead
nitrate may modify the production of TNF-alpha in response to endogenous LPS of intestinal origin. An enhanced production of TNF-alpha could therefore be involved in the mitogenic action of lead nitrate. EXPERIMENTAL
DESIGN: We investigated first whether a single intravenous dose of lead nitrate (100 mumole/kg) to rats modifies the production of HGF, TGF-alpha, and TGF-beta1, by examining the steady-state level of their mRNA in the liver by Northern blot analyses. The response of rats given lead nitrate to various doses of LPS was next evaluated to determine whether lead-treated rats have an enhanced sensitivity to LPS. Finally, the level of TNF-alpha mRNA was examined in the liver of rats at various time periods after a single injection of lead nitrate. RESULTS: No changes were observed in the liver levels of mRNAs for HGF, TGF-alpha, and TGF-beta1 at various time intervals after a single injection of lead nitrate. All rats given only single injections of LPS up to 100 mug survived. However, lead nitrate-treated rats tolerated LPS at dosages of only 6 mug. The liver of control rats showed a single 1.6 kb TNF-alpha transcript, whereas 1.8-kb transcripts were seen at 1 hour after lead nitrate injection, and persisted for 12 hours. The 1.8 kb TNF-alpha transcript was also present in the spleen of control rats, and its expression was enhanced in lead nitrate-treated rats. CONCLUSIONS: Stimulation of hepatocyte proliferation
induced by lead nitrate was not accompanied by changes in liver levels of HGF, TGF-alpha, or TGF-beta1 mRNA. Lead nitrate, however, enhanced expression of TNF-alpha at a time preceding the onset of hepatocyte DNA synthesis, indicating that TNF-alpha may trigger the lead nitrate-induced proliferation of hepatocytes.

8/7/104 (Item 51 from file: 73)
DIALOG(R)File 73:EMBASE

05701680 EMBASE No: 1994108089
rac p21 is involved in insulin-induced membrane ruffling and rho p21 is involved in hepatocyte growth factor- and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced membrane ruffling in KB cells
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Molecular and Cellular Biology (MOL. CELL. BIOL.) (United States) 1994, 14/4 (2447-2456)
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Insulin and hepatocyte growth factor (HGF) induced morphologically different membrane rufflings in KB cells. Insulin-induced membrane ruffling was inhibited by microinjection of rho GDI, an inhibitory GDP/GTP exchange regulator for both rho p21 and rac p21 small GTP-binding proteins, but not inhibited by microinjection of botulinum exoenzyme C3, known to selectively ADP-ribosylate rho p21 and to impair its function. This rho GDI action was prevented by comicroinjection with guanosine 5'-(3-O-thio)triphosphate (GTPgammaS)-bound rac1 p21. In contrast, HGF-induced membrane ruffling was
inhibited by microinjection of rho GDI or C3. This rho GDI action was prevented by comicroinjection with GTPgammaS-bound rhoA p21, and this C3
action was prevented by comicroinjection with GTPgammaS-bound rhoA(Ile-41)
p21, which is resistant to C3. Microinjection of either GTPgammaS-bound rac1 p21 or rhoA p21 alone induced membrane ruffling in the absence of the growth factors. The rac1 p21-induced membrane ruffling was morphologically
similar to the insulin-induced kind, whereas rhoA p21-induced ruffling was apparently different from both the insulin- and HGF-induced kinds. Membrane
ruffling was also induced by 12-O-tetradecanoylphorbol-13-acetate (TPA), a protein kinase C-activating phorbol ester, but not by Casup 2sup + ionophore or microinjection of a dominant active Ki-ras p21 mutant (Ki-ras(Val-12) p21). The phorbol ester- induced membrane ruffling was morphologically similar to the rhoA p21- induced kind and inhibited by microinjection of rho GDI or C3. These results indicate that rac p21 and rho GDI are involved in insulin-induced membrane ruffling and that rho p21 and rho GDI are involved in HGF- and phorbol ester- induced membrane rufflings.

8/7/105 (Item 52 from file: 73)
DIALOG(R)File 73:EMBASE

05655944 EMBASE No: 1994069130
Acute liver failure
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Acute liver failure is a multiorgan syndrome with dramatic clinical features and, often, a fatal outcome. It is characterized by the onset of coma and coagulopathy within 6 months, and usually in <6 weeks, from onset of illness. Viral hepatitis, drug-related liver injury, and the alcohol-acetaminophen syndrome are the most common etiologies. Altered mental status accompanied by jaundice is a hallmark of acute liver failure. A unique feature is the evolution of increased intracranial pressure due to cerebral edema. The resulting cerebral ischemia and brainstem herniation account for approximately 50% of deaths in patients with acute liver failure. Mannitol therapy may successfully treat most patients with high intracerebral pressure. Most patients demonstrate features of the multiple organ failure syndrome, including a shock-like state, renal failure, and occasionally respiratory distress syndrome. Close monitoring of volume status is necessary, since administration of large quantities of fluid may be required. %%%Infection%%% is also common; most pathogens are gram-positive, and fungal %%%infections%%% are also seen. Because an optimum therapy for acute liver failure does not yet exist, liver transplantation should be considered early, before advanced levels of coma develop. Alternative, experimental treatment modalities include heterotopic liver grafting, administration of hepatocyte growth factor, use of an extracorporeal liver-assist device, and liver cell transplantation, but none of these has attained widespread use.

8/7/106 (Item 53 from file: 73)
DIALOG(R)File 73:EMBASE

05423385 EMBASE No: 1993191484
The protooncogene c-sea encodes a transmembrane protein-tyrosine kinase related to the Met/hepatocyte growth factor/%%%scatter%%% %%%factor%%%

receptor

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c-sea is the cellular homologue of the avian erythroblastosis virus S13-encoded oncogene v-sea. We have isolated and determined the nucleotide sequence of overlapping chicken cDNAs that encode the putative c-sea protooncogene product. The predicted reading frame encoded a 1404-aa polypeptide that had the structure of a receptor-like protein-tyrosine kinase and exhibited the highest degree of sequence similarity with the Met/hepatocyte growth factor/%%%scatter%%% %%%factor%%% receptor. Analysis
of steady- state RNA expression revealed that c-sea mRNA levels were elevated approx. eq.5-fold in chicken embryo cells transformed by activated variants of the src nonreceptor protein-tyrosine kinase gene but not in cells transformed by the nuclear oncogenes v-myc or v-rel. A survey of c-sea expression in a variety of chicken tissues indicated that the highest levels of mRNA were located in peripheral white blood cell populations and in the intestine.

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DIALOG(R)File 98:General Sci Abs/Full-Text

04045913 H.W. WILSON RECORD NUMBER: BGSI99045913 (THIS IS THE FULLTEXT)
Functions of cell surface heparan sulfate proteoglycans.
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Gotte, Martin; Park, Pyong Woo
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ABSTRACT: The heparan sulfate on the surface of all adherent cells modulates the actions of a large number of extracellular ligands. Members of both cell surface heparan sulfate proteoglycan families, the transmembrane syndecans and the glycosylphosphoinositide-linked glypicans, bind these ligands and enhance formation of their receptor-signaling complexes. These heparan sulfate proteoglycans also immobilize and regulate the turnover of ligands that act at the cell surface. The extracellular domains of these proteoglycans can be shed from the cell surface, generating soluble heparan sulfate proteoglycans that can inhibit interactions at the cell surface. Recent analyses of genetic defects in Drosophila melanogaster, mice, and humans confirm most of these activities in vivo and identify additional processes that involve cell surface heparan sulfate proteoglycans. This chapter focuses on the mechanisms underlying these activities and on the cellular functions that they regulate.
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TEXT:

Key Words glypicans, syndecans, extracellular matrix, growth factors, cell adhesion

INTRODUCTION

Components of the extracellular environment direct cell proliferation, differentiation, migration, and changes in cell shape. These components exert their effects on cells by binding to highly specific cell surface receptors, which, when occupied, are internalized or transduce intracellular signals. These receptors transmit signals into the cell and often use cell surface heparan sulfate (HS) to recognize their ligands or to regulate their activation. A strongly anionic linear polysaccharide, HS has been known since it was distinguished by its lower extent of sulfation from the pharmaceutical product heparin (1). Like heparin, HS chains are structurally heterogeneous and avidly bind a diverse repertoire of proteins under physiological conditions. Cell surface HS provides cells with a mechanism to snare a wide variety of extracellular effectors without requiring multiple novel binding proteins. Although HS has been known to be ubiquitous at animal cell surfaces for nearly 30 years (2, 3) and is generally more abundant at the cell surface than most receptors, it has only relatively recently been appreciated for these activities.

HS is synthesized on a variety of cell surface proteins but is found consistently on members of two major families of membrane-bound proteoglycans (PGs), the syndecans and the glypicans. The prototype cell surface heparan sulfate proteoglycan (HSPG), syndecan-1, was first identified as a developmentally regulated type-I transmembrane protein that
bound extracellular-matrix (ECM) components to epithelial cells (4, 5, 102). It was named syndecan, from the Greek "syndein," to bind together, because it was thought to link the ECM components to the actin-containing cytoskeleton (6). Structurally related syndecans were soon identified (reviewed in 8), as was a distinctive cell surface HSPG that was linked directly to membrane phospholipid (7). This glycosyl phosphatidyl inositol (GPI) linkage is the origin of the name glypican, and several additional structurally related glypicans have been identified. Each syndecan and glypican gene product bears HS chains as a constant feature, in contrast to so-called part-time PGs, that may bear HS chains in some proportion or under some conditions (e.g. CD-44, betaglycan).

By way of their HS chains, syndecans and glypicans can bind a wide variety of soluble and insoluble extracellular ligands (Table 1). Binding is relatively high affinity (Kd of 1-100 nM) and generally resistant to physiological salt concentrations (8, 9). Much evidence suggests that these interactions are not fortuitous, but functional. Organizing the currently identified proteins by their major functions indicates that a large number are involved in morphogenesis and wound repair, host defense, and energy metabolism. (Table 1) The cell surface HSPGs can enhance the formation of receptor-ligand signaling complexes, can direct ligands into the cell for degradation or recycling, and can themselves be shed from the cell surface as soluble PGs. This shedding can be part of HSPG turnover but can also be accelerated by effectors, generating potent soluble HSPG inhibitors and cells that are less responsive to ligands.

This review focuses on the functional interactions of syndecans and glypicans and on the biological activities they regulate. However, before addressing these topics, we briefly discuss HS biosynthesis, the molecular strategies of both the HS and protein components of these PGs, and their expression. Much recent work recapitulates for other ligands the interaction of cell surface HS with antithrombin III. Studies on this interaction are remarkably prescient in finding a distinctive HS sequence for binding, HS-mediated molecular encounters, and specific HS sulfotransferase isoforms (10-12). These and other details not covered owing to space limitations will be found in several excellent recent reviews (Table 2).

HEPARAN SULFATE BIOSYNTHESIS

The highly diverse structure of HS chains has been known for some time (for
reviews, see 14). Recent molecular cloning of many of the biosynthetic enzymes has led to improved understanding of the basis for HS chain structural complexity, tissue-specific differences, and the tailoring of sequences for interactions with defined proteins (14). HS is synthesized by (a) formation of a region linking the HS chain to protein, (b) generation of the polysaccharide chain, and (c) enzymatic modification of the chain to yield the specific saccharide sequences and structural organization that are responsible for protein binding (Figure 1).

CHAIN INITIATION

The initial step in the formation of the tetrasaccharide linkage region (-GlcA-Gal-Gal-Xyl-Ser) is the transfer of xylose from UDP-xylose to the hydroxyl group of specific serine residues on the core protein. This linkage region is identical for both HS and chondroitin sulfate (ChS) chains and is likely produced by the same enzymes. A distinct transferase then adds a single GlcNAc residue to the nonreducing end of the linkage region. This enzyme distinguishes between sites on the core protein intended for glycosylation with HS chains, initiated with GlcNAc, from those sites to be glycosylated with ChS chains. This enzyme (GlcNAc Transferase I) has not yet been cloned, and the precise core protein sequence that establishes the HS attachment site is not yet clear (15). Indeed, initiation with GalNAc and elongation of a ChS chain appear to be the default pathway.

CHAIN MODIFICATION

Alternating addition of GlcA and GlcNAc from their respective UDP-sugar nucleotide precursors by a single HS polymerase forms the repeating 1,4-linked disaccharide HS chain (16, 17). The length of the HS chains can vary over 10-fold with cell type and core protein, but the chain termination mechanisms are mostly unknown. Once the HS chain is assembled,
generally 50-150 disaccharides, the individual saccharide units are subjected to a series of sequential enzymatic modification reactions in which the products of one reaction are substrates for the next. These reactions apparently do not convert all of the available substrate, resulting in substantial sequence diversity in the final chain. The initial modification enzyme is the N-deacetylase/N-sulfotransferase that replaces the N-acetyl group of Glc-NAc residues with a sulfate group (18, 19). The enzyme modifies clusters of Glc-NAc residues, leaving regions of the chain unmodified. The extent of this modification varies among the distinct N-deacetylase/N-sulfotransferase enzymes from rat liver, mouse mastocytoma,
and trachea (20-22). Then D-glucuronic acid residues adjacent to GlcNSO3 residues are epimerized to L-iduronic acid units by glucuronyl C-5 epimerase (23).

These modified disaccharides will receive the bulk of the subsequent O-sulfations. An iduronosyl 2-O-sulfotransferase (2-OST) acts, then a glucosaminyl 6-O-sulfotransferase (6-OST) acts, and the modification reactions are completed with modification of a few residues by glucosaminyl 3-O-sulfotransferase (3-OST) (for reviews, see 12, 24). The sulfotransferases use 3'-phosphoadenosine 5'-phosphosulfate as a sulfate donor. The 3'-phosphoadenosine 5'-phosphosulfate is synthesized from ATP and SO3 via a single enzyme having both ATP sulfurylase and adenosine 5'-phosphosulfate (APS) kinase activities (25). Each of these sulfotransferases has multiple isoforms, some of which are tissue specific, share distinct substrate specificities, or both. For example, GlcA-2-SO3 is a relatively minor component of HS except in brain, suggesting a tissue-specific sulfotransferase (14).

DOMAIN STRUCTURE

Because the modification reactions are clustered around the GlcNSO3-containing disaccharides, the highly sulfated regions of the chain form blocks of 6-10 disaccharides that resemble heparin in structure (26). These highly sulfated domains (HSD) alternate with larger regions of the chain (16-20 disaccharides) that are largely unmodified. The boundary between the HSD and the unmodified domains (UMD) is not sharp and may consist of short mixed sequences where N-acetylated disaccharides alternate
with N-sulfated ones (27). This macroscopic structure of HSD alternating with UMD can differ between HS chains derived from different cell types (28, 29). The relatively rigid, highly anionic HSDs have facile access to basic residues on protein surfaces because of the adjacent more flexible UMDs. Thus, the binding avidity of HS chains for proteins can vary with the spacing of these domains.

This biosynthetic scheme leads to enormous structural heterogeneity in which no two chains are identical (14). The scheme and overall HS structure seem to be conserved from flies to humans, in contrast to major differences between species in the composition and structure of other complex carbohydrates (A Varki, unpublished data). Moreover, the saccharide sequence is informational as certain protein ligands bind most avidly only to specific sequences (13, 276). Finally, HS chains from different cell types (28, 29) and tissues (26, 30) vary reproducibly, possibly owing to activity differences of cell type-specific isozymes (12, 24). Indeed, HSPG from developing mouse neuroepithelium rapidly changes its fibroblast growth factor (FGF)-binding selectivity (31) owing to a change in HS structure (32).

MOLECULAR DESIGN OF CELL SURFACE HEPARAN SULFATE PROTEOGLYCANS

HSPGs sequester proteins within secretory vesicles, link proteins together within the ECM, as well as bind proteins to the cell surface. The HSPG at each site contains different core proteins. The HSPG within mast cell granules is the source of heparin, the pharmaceutical product. Most ECM-associated HS is on the basement membrane PGs, perlecan, (see 33 for review), agrin and type-XVIII collagen (277). The core proteins of cell surface HSPGs dictate the cellular location and metabolism of their HS chains. These HS chains are responsible for much of the biological role of the HSPGs, and their core proteins have evolved to maximize their efficiency in these roles.

HEPARAN SULFATE CHAINS

HS arose early during metazoan evolution and is at the surface of all adherent animal cells. HS is present in lower invertebrates, including organisms diverging as early as Cnidaria but, interestingly, not in the more primitive Porifera (34). Based on the presence of HS in these primitive metazoans, it appears that it arose in the pre- and early Cambrian period. This was concurrent with the emergence of the basic aspects of epithelial organization that led to the segregation of an intercellular milieu and to the subsequent appearance of ECM components and
signaling molecules. Indeed, the ancestral HSPGs may have functioned to generate these epithelial sheets. Because various proteins involved in organizing the basic body plan depend on interaction with HS for their function (see Table 1), HS likely became important when these processes became evident. Indeed, since then, no new basic body plan has evolved, and HSPGs have become major constituents of processes that are important for metazoan survival. This suggests that HSPGs have acquired their current role by variation and selection, the mechanism widely used in biology to generate complex organization (35).

HS chains on the same core protein from different cell types can show consistent and reproducible structural differences such as variations in domain number, spacing, or size and in their O-sulfation pattern (29). Where examined, various ligands bind selectively to specific HS sequences, for example, FGF-1, FGF-2, transforming growth factor (TGF)-b, platelet factor 4, and others (14, 36). Other ligands may have specific sequence requirements, but progress in establishing these recognition sequences has been slow because of the extensive structural diversity of HS chains and cumbersome sequencing technology.

Proteins bind to HS via basic residues on their surfaces, mostly via distinct protein domains. Because HS has remained relatively constant in structure, those proteins whose function depends on interactions with HS retained the ability to bind HS. Protein domains of recent evolutionary origin are readily identified by their sequence resemblance, but because the resemblance may have eroded over evolutionary time, domains that arose during ancient times may only be apparent after three-dimensional structural analysis (37). Some HS-binding proteins contain linear clusters of basic residues often in a distinct pattern (38), but most differ in their HS-binding sequences. Indeed, there is no consensus HS-binding sequence motif, suggesting that many of the binding domains are ancient.

Cell surface HS modulates ligand-receptor encounters as has been well shown by studying responses of cells made defective in HS biosynthesis by mutations in biosynthetic enzymes (39). Cell surface HS can immobilize the ligand, increase its local concentration, change its conformation, present it to a signaling receptor, or otherwise modify the molecular encounters between ligands and receptors. The overall effect is usually to enhance receptor activation at low ligand concentrations (40). Although this coreceptor role (8) has received much verification, the mechanism by which HS acts is not always clear.

An attractive hypothesis for the diverse roles of cell surface HS is that the chains catalyze molecular interactions at the cell surface (41, 42). The idea is based on the well-studied effect of heparin on the serpin AT III, in which heparin accelerates by several orders of magnitude the rate at which this inhibitor inactivates the serine protease thrombin. The heparin provides a surface on which the reactants encounter each other at a much greater rate than they could in solution (an effect of reduced dimensionality). The HS chains can enhance peptide diffusion, establish concentration gradients, and accelerate encounters even for soluble factors that do not have high affinity for heparin/HS (41). Rate enhancement owing to HS-mediated accelerated molecular encounters has been applied to growth
factor interactions with their receptors (42). This model can explain the hyperbolic potentiation of growth factor activity often seen with increasing heparin/HS concentrations. Stimulation of activity at low concentrations would be owing to reduced dimensionality, whereas the reduction in activity at high concentrations would be owing to the large number of surfaces to which the growth factor can bind. The effect of cell surface HS will vary depending on relative abundance of the HS chains and the reactants, their relative affinities, and the size and nature of the HS chain.

FUNCTIONAL INTERACTIONS OF HEPARAN SULFATE PROTEOGLYCAN CORE PROTEINS

The HS chains at the cell surface are mostly attached to syndecan and glypican core proteins (Figure 2). These core proteins determine the

proximity of the HS chains to the cell surface; when, where, and to what extent the HS chains are expressed; and the rate and mechanism of HS turnover. Some domains of these proteins are remarkably stable throughout evolution, implying highly specific functional interactions.

Syndecan Core Proteins The syndecan core proteins comprise a family of four distinct genes in mammals. Their chromosomal locations, exon organization, and sequence relationships with the single Drosophila syndecan (D syndecan) suggest that the gene family arose by gene duplication and divergent evolution from a single ancestral gene, and that syndecan-1 and -3 and syndecan-2 and -4 represent subfamilies (reviewed in 8). Each gene product is a single type I membrane-spanning protein with an apparently extended extracellular domain of varying size that contains covalently attached HS chains distal from the plasma membrane (Figure 2).

In addition to a signal sequence, the syndecan core proteins contain at least eight functional domains (see details in 8) (Figure 3). The extracellular domains (ectodomains) are among the most rapidly diverging vertebrate proteins with the exception of their regions for (a) GAG attachment, (b) cell interaction, (c) proteolytic cleavage, and (d) oligomerization. The transmembrane domains are relatively stable evolutionarily; only a few amino acids differ among the vertebrate sequences. These domains contain (e) regions for interactions with other membrane proteins and for localization to distinct membrane compartments. The cytoplasmic domains contain two invariant regions, (f) a membrane proximal common region (C1) containing a serine and a tyrosine and (g) a C-terminal common region (C2), separated by (h) a region (V) of variable length and composition. The V region in specific syndecans is highly conserved among vertebrate species. These relationships suggest that each syndecan family member interacts with the same proteins (transmembrane domain and C regions) yet also has unique interactions (ectodomain and V region).

Ectodomains. The ectodomains contain two regions for GAG attachment. A
region near the N terminus that, by homology with syndecan-1, consistently bears HS chains (43). This region contains two or three consecutive ser-gly sequences flanked by hydrophobic and acidic residues, the canonical sequence for HS attachment (15, 44). Syndecan-1 and -3 also contain ser-gly sequences near the plasma membrane that may serve as attachment sites for
ChS (43). Syndecan-4 may also bear ChS chains.

The syndecan-4 ectodomain core protein has a high-affinity binding site for an unknown ligand on the surfaces of several human and mouse cell types, whereas the syndecan-1 core protein ectodomain shows weak binding to
the surface of Swiss 3T3 cells (45). Syndecan-4 binding to cells is specific, because the chick syndecan-4 ectodomain, but not other mammalian ectodomains, can block this binding. Syndecan-4 binding is avid (Kd of 2 nM), and the cell-binding domain maps in the 120-residue mouse syndecan-4 ectodomain to a 54-amino-acid sequence that lies proximal to the GAG attachment site (46).

All syndecans studied can be shed from the cell surface by proteolytic cleavage near the plasma membrane (47). Shedding of the syndecan ectodomains is highly regulated and can be accelerated by various cellular effectors, which, interestingly, do not usually bind HS. Thrombin or plasmin may cleave at a mono- or dibasic site adjacent to the plasma membrane in the vertebrate syndecans (48). However, the site endogenously cleaved by the cell is within 5 amino acids of the plasma membrane because substitution of these amino acids in syndecan-1 with the same region of CD4, the T-cell transmembrane protein which is not endogenously shed, prevents the shedding (Z Wang, M Bernfield, unpublished data).

Transmembrane Domains. The transmembrane domain may localize the syndecans into discrete membrane microdomains. For example, syndecan-1 polarizes to the basolateral cell surface of epithelia, whereas syndecan-4 localizes to focal adhesions (49-51). The transmembrane domains may also interact within the plane of the membrane with proteins involved in cell spreading, because cells containing syndecan-1 or -4 devoid of their cytoplasmic domains can still attach and spread on substrata, and this spreading is sensitive to protein tyrosine kinase inhibitors (52, 53).

Cell surface receptors that activate intracellular signaling pathways commonly oligomerize (54). First suspected when the apparent molec-ular size of the GAG-free core proteins on polyacrylamide gel electrophoresis far exceeded their actual size (6), all syndecans seem to be able to form sodium dodecyl sulfate (SDS)-resistant oligomers, especially dimers. That these PGs form oligomers is surprising considering the molecular volume of their HS chains. HS chains can self-associate (55), but it is not clear whether the HS chains affect oligomerization. Indeed, oligomers are most readily demonstrated by syndecans bearing relatively small HS chains (i.e. produced by keratinocytes) or by syndecans devoid of HS chains (56). Oligomerization would enhance the proximity between syndecan core proteins,
enlarging their interaction surface, and increasing the probability of interaction with other membrane proteins (54). This could be the mechanism by which syndecans associate with the actin cytoskeleton-after antibody-induced or insoluble ligand-induced clustering (syndecan-1 and -3) (57, 58).

Glycine residues interspersed among the bulky hydrophobic amino acids in the region that corresponds to the outer membrane leaflet in the transmembrane domain have been proposed to regulate syndecan oligomerization (60). Work with syndecan-3 suggested that these glycines impose a helical conformation on this domain and that, together with highly basic residues in the juxtamembrane region, this conformation facilitates formation of core protein oligomers (58). However, if the spurious migration on polyacrylamide gel electrophoresis is caused by oligomers, the juxtamembrane basic amino acids are not essential for oligomer formation because Drosophila syndecan also migrates spuriously but does not have these amino acids (61). Moreover, the shed ectodomains, free of transmembrane domain, migrate similarly to the intact PGs on polyacrylamide gel electrophoresis, suggesting that they too form oligomers.

Cytoplasmic Domain. The C1 region of the cytoplasmic domain is rich in basic residues as would be expected for a stop transfer function. However, the nearly identical sequence in all family members from both vertebrate and invertebrate origins suggests a sequence-specific function. The region bears close sequence homology with the identical regions of neurexin I/III and somewhat less homology with glycophorin C, both type-I membrane proteins that contain PDZ-binding motifs at their C-termini and both associated in some way with the cytoskeleton (76), like the syndecan core proteins (62). Phosphorylation of the invariant serine in the C1 region has been detected in the syndecan-4 core proteins (67). Taken together, the C1 region of each syndecan may be involved in the formation of cytoplasmic signaling complexes.

The C1 region of syndecan-3 binds a protein complex from neuroblastoma cell extracts composed of the Src family kinases, C-Src and C-Fyn, the Src substrate and actin-binding protein cortactin, tubulin, and an unidentified 30-kDa protein (68) (Figure 4). The Src family kinases are multidomain cytoplasmic proteins that have tyrosine-specific protein kinase activity, can be phosphorylated, and undergo extensive inter- and intramo-lecular interactions in the process of mediating signals from a variety of cell surface receptors (see 69 for review). Importantly, when syndecan-3 on the neuroblastoma cells binds the heparin-binding growth-associated molecule (also known as pleiotropin and as midkine), an adhesion molecule found in the developing brain, neurite outgrowth is enhanced, and both Src and cortactin are phosphorylated (68). Details of the molecular events remain to be established, but these data suggest that syndecan binding to an adhesion molecule at the cell surface involves the association of the C1 domain with C-Src and C-Fyn, the same molecules that are activated by engagement of integrin receptors by fibronectin and that localize to focal adhesions upon cell adhesion (69). A similar mechanism is likely in other cells and with other syndecans because C-Src and C-Fyn are ubiquitously expressed and the C1 region is common to all syndecans.

The V regions differ among the family members in both size and sequence, suggesting functional differences between these PGs. Binding to ECM immobilizes syndecan-4 in the membrane, enabling its V region to bind both the catalytic domain of protein kinase Ca (PKC)-a, activating this Ser/Thr kinase (59, 70), and phosphatidyl inositol-4,5 bis phosphate (PtdIns-4,5-P2) (59, 70), which both promotes oligomerization of the cytoplasmic domain (59, 71) and results in calcium independence of PKC-a (Figure 5). PKC-a activation causes focal adhesions to form (73) and syndecan-4 to accumulate in them (74). PtdIns-4,5-P2 levels increase after integrin ligation and control cytoskeletal rearrangements via the Rho family of GTP-binding proteins (75). In contrast to these activations, the V regions of syndecan-2 serve only as a substrate for PKCa and protein kinase A (63, 64, 66).

The C2 regions have an EFYA sequence at their C terminus that can bind to PDZ domain-containing proteins (Figure 4). PDZ domains, named for PSD-95, Discs-large, and Zonula occludens-1 proteins, bind specific C-terminal sequences and organize and assemble protein complexes at the inner face of the plasma membrane (76) and are thought to link membrane components to the underlying actin-containing cytoskeleton. This interaction may account for the variety of changes in actin filament organization associated with the syndecans, including binding of syndecan-1 to a crude preparation of F-actin filaments (77), colocalization of syndecan-1 and F-actin at the basal surfaces of polarized mammary

epithelial cells (reviewed in 78), actin filament reorganization on engagement of the syndecans with an ECM ligand (79), or on depletion of syndecan-1 from epithelial cells (80). Stable expression of syndecan-1 in cultured Schwann cells, which normally do not express syndecan-1, results in actin microfilament reorganization and transient colocalization of cell surface syndecan-1 and F-actin during cell spreading (81). The distribution of this clustered syndecan-1 is altered by cytochalasin treatment (57) and requires the cytoplasmic domain (82). Clustering of cell surface syndecan-1 with FGF-2- or collagen I-coated beads, or by antibodies, also leads to recruitment of actin microfilaments (40).

Recent studies with the yeast two-hybrid system provide the initial molecular explanations for these actin cytoskeleton interactions (83-85). A novel and widely distributed 33-kDa protein containing two class II PDZ domains, named syntenin, binds at high affinity to the syndecan C terminus (83). When expressed in CHO cells, GFP-syntenin and mouse syndecan-2 colocalize at the plasma membrane and in intracellular vesicles. High expression of GFP-syntenin results in the formation of cell surface projections and a flattened cell morphology, consistent with a role of syntenin in cytoskeleton organization (83). A similar function has been ascribed to CASK, a PDZ-domain protein, which also binds to the EFYA motif (84). CASK is a 120-kDa membrane-associated guanylate kinase homology (MAGUK) protein that is the ortholog of LIN-2A, a Caenorhabditis elegans scaffolding protein. CASK colocalizes with syndecan-1 in a variety of epithelial tissues, colocalizes with syndecan-2 in rat brain synapses, and can be coimmunoprecipitated with rat syndecan-2 from COS-7 cells expressing both proteins (85). CASK contains a binding site for protein-4.1 family members, which include ERM (ezrin, radixin, moesin) proteins and talin, each known to associate with the actin cytoskeleton (Figure 4). Protein 4.1 may bind directly to syndecan cytoplasmic domains (62). Thus, although other components will certainly be described, current evidence places the syndecan cytoplasmic domains within an organized complex of subplasmalemmal scaffolding proteins.

PHOSPHORYLATION The invariant serine and three invariant tyrosine residues in cytoplasmic domains can be phosphorylated by using approaches from synthetic peptides to cultured cells manipulated with phosphatase inhibitors (63, 64, 66). The need for the phosphatase inhibitors suggests rapid turnover of a relatively small pool of phosphor-ylated syndecan cytoplasmic domains. The invariant serine and tyrosine residue of syndecan-4 are phosphorylated endogenously (67, 86). Interestingly, the serine appears to be dephosphorylated in response to FGF-2 (86), which allows oligomerization and binding of PtdIns-4,5-P2 and PKCa (87). This may explain how ECM modifies the action of growth factors including FGF-2 (88) (Figure 5).

Inhibitor studies suggest that Src family kinases phosphorylate the syndecans, but which of the tyrosines is phosphorylated is not yet known. Phosphorylation of the tyrosine residue in the EFYA motif might negatively regulate the interaction of syndecans with PDZ-domain proteins like CASK or syntenin. Indeed, an undesignated cytoplasmic domain tyrosine residue was found to be critical for the association of syndecan-1 with the actin cytoskeleton (82).

Glypican Core Proteins The glypicans comprise a family of at least six distinct genes in mammals (Figure 6). All of the structural features of these proteins are shared by the product of the dally (division abnormally delayed) gene in D. melanogaster (89). All glypicans share (a) an N-terminal signal sequence, (b) an [similar]50-kDa domain containing a characteristic pattern of 14 highly conserved cysteine residues, (c) a presumably extended region near the plasma membrane that contains 2 or 3 Ser-Gly GAG attachment sequences of the type described above for the syndecan core proteins, and (d) a C-terminal sequence involved in formation of a glycosyl phosphatidyl inositol (GPI) linkage to the plasma membrane. Sequence relationships and exon organizations suggest that glypicans consist of three subfamilies, glypicans-1 and -2, glypicans-3 and -5, and glypicans-4 and -6 (90, 281).

The distinctive features of the glypicans are the cysteine-rich domain, the apparently close proximity of the HS chains to the plasma membrane, and the GPI anchor. The core protein region of 14 conserved cysteine residues suggests a disulfide-linked compact and possibly globular domain that functions in protein-protein interactions. Except for the HS attachment sequences, the HS-bearing juxtamembrane regions are the most divergent sequences in these core proteins.

Interactions With Membrane Lipid. Glypicans are linked to membrane lipid without penetrating the bilayer. The GPI-anchored proteins in mammalian cells generally associate via their saturated acyl chains with ordered regions of membrane lipid that resist solubilization by nonionic detergents in the cold (91, 93). These regions ("rafts") are rich in cholesterol and glycosphingolipid, are rather uniformly distributed throughout the plasma membrane, and have no readily discernible morphological correlate (91).

The GPI anchor is thought to associate with specific membrane microdomains on the apical surfaces of polarized cells (e.g. within lipid rafts of epithelia and endothelia). When examined, however, glypican-1 polarized to the basolateral surface of cultured epithelia. Sequential deletion of the HS attachment sites increased the extent of apical targeting, and when no HS glycosylation was possible, the GAG-free glypican-1 was exclusively on the apical surface (92). Thus, glypican-1 distribution on the cell surface was determined primarily by the extracellular interactions of its HS chains with basal ECM, but apical sorting predominated in the absence of these interactions.

Uptake and Metabolism. The GPI anchor is reported to mediate the turnover of cell surface components by rapid endocytosis and transport to lysosomes (93). This is consistent with findings in ovarian granulosa cells in which a glypican is endocytosed and completely degraded within 30 min without detectable intermediates (reviewed in 94). However, in endothelial cells and fibroblasts, a substantial proportion of the GPI-linked HSPG appears to be internalized to the cytoplasm, endosomal compartments, or the opposite cell surface while the ligand and PG are recycled back to the cell surface (reviewed in 95, 109). This pathway may be critical for the internalization and recycling of proteins bound to cell surface HS, for example, AT III (96), tissue factor pathway inhibitor (97), extracellular superoxide dismutase (98), and follistatin (99).

Shedding. Glypicans can be released from cell surfaces by proteolytic cleavage and by the action of a phosphatidyl inositol-specific phospholipase C (100). Indeed, glypican-1 can be found in the conditioned media of cultured cells either intact (presumably cleaved by phosphatidyl inositol-specific phospholipase C) (101) or without membrane lipid (presumably cleaved by protease) (7; reviewed in 90), but it is not known whether this generation of soluble glypicans is a regulated or physiological process. One potential mode of regulation is acylation of the membrane-linked inositol of the GPI anchor, which would increase its resistance to cleavage by phosphatidyl inositol-specific phospholipase C (103). After release, the now soluble glypican has been reported to bind to a cell surface receptor and be endocytosed (100), but the quantitative significance of this pathway and the putative receptor have not been defined.

SYNDECAN VERSUS GLYPICAN MOLECULAR STRATEGIES

The existence of two distinct gene families of cell surface HSPGs implies that they subsume distinct functions, but few studies have established family-specific functions. However, distinct molecular strategies can be deduced from their different structures. The cysteine-rich glypican ectodomains differ markedly from the proline-rich syndecan ectodomains in that the former are likely globular and the latter are likely highly extended proteins.

The site of GAG chain attachment on the core protein appears to influence HSPG function. Expression of syndecans replete with HS chains markedly reduces the invasion of leukemia cells into type-I collagen gels (104). However, expression of glypican-1 fails to reduce invasion although it is similarly glycosylated with HS chains. Expression of syndecan-glypican chimeras shows that inhibition of invasion resides in the syndecan ectodomain, presumably owing to interactions of the core protein with other cell surface molecules or the distal placement of the HS chains or both (105). On the other hand, both syndecan-1 and glypican-1 are effective in binding FGF-2 to the FGF-R1 and in mediating FGF-R1 activity in response to FGF-2 (106).

The ectodomains of cell surface HSPGs are shed into extracellular spaces. Each of the syndecan ectodomains is constitutively shed from cultured cells by proteolytic cleavage of the core protein. At least for syndecans-1 and -4, the shed ectodomain is in body fluids, indicating that syndecan shedding is physiological (48, 107, 245). Glypican ectodomains are found in cell culture media but whether glypicans are shed physiologically is unknown.

The way in which the HSPGs associate with the membrane can determine their and their ligand's metabolic fate. Indeed, the kinetics of turnover for GPI-linked and transmembrane HSPGs seem to differ on the same cell (94). Ligands internalized via glypicans may enable the receptor and ligand to recycle (109), analogous to the metabolism of antithrombin III at endothelial cell surfaces (12). Syndecans and their ligands are likely

endocytosed by noncoated pit pathways into lysosomal compartments in which
the PG and ligand are degraded. Lipoprotein lipase appears to be handled in this manner at capillary endothelial surfaces (110).

A cytoplasmic domain enables the syndecans to associate with cytoskeletal proteins and signaling molecules, whereas glypicans can send information across the membrane into the cell only by binding transmembrane
proteins that have signaling capability (reviewed in 93). Because insoluble ligands potentiate cytoplasmic domain interactions, formation of signaling complexes with these ligands is probably limited to syndecans.

REGULATION OF CELL SURFACE HEPARAN SULFATE PROTEOGLYCAN EXPRESSION

Virtually all adhesive cells express at least one syndecan, and most express multiple syndecans (47). Glypicans are expressed predominantly in the central nervous system (CNS), and except for glypican-2, are also expressed in nonneural cells. Each syndecan and glypican family member is expressed in a distinct cell-, tissue-, and development-specific pattern, suggesting different functions. Syndecan (see 111 for review) and glypican (see 90 for review) expression has been extensively studied during mouse embryogenesis (Tables 3 and 4). Briefly, syndecan-1 appears first, during cleavage stages, and undergoes major changes in expression during the epithelial-mesenchymal interactions responsible for development of various organs. Syndecan-3 and glypican-1 appear next, predominantly in limb and neural crest-derived mesenchyme, and undergo changes in expression with cell migration and proliferation.

Many inducers of syndecan expression are themselves ligands, suggesting that syndecan induction provides a means of regulating their activity. For example, FGF-2 alone (112) or in combination with TGF-b1, enhances syndecan-1 expression in 3T3 cells (113); platelet-derived growth factor or angiotensin II induces syndecan-1, and TGF-b1 induces syndecan-2 in vascular smooth muscle cells (114). Alternatively, because syndecan induction generally leads to increased levels of shed syndecan ectodomains, the induction could neutralize the action of the inducer; for example, the shed ectodomain could bind the inducer and prevent its action. Interestingly, the TGF-b1 and FGF-2 combination has no effect on syndecan-1
levels in human lung fibroblasts but reduces glypican-1 levels by nearly half (115). The antimicrobial peptide PR-39 induces syndecan-1 and -4 expression in cultured mesenchymal cells (116). In contrast, TNF-a decreases syndecan-1 expression in cultured endothelial cells (117).

Potential binding sites for several transcription factors have been identified in the upstream sequences of cell surface HSPG genes (118-124). In addition to NF-B, Myo-D, and Antennapedia-binding sites, the syndecan-1 promoter has multiple proximal Sp-1 binding sites, likely accounting for its high level of constitutive expression in epithelial cells. Its expression in skeletal myoblasts is controlled by a proximal promoter region that is influenced by FGF-2, TGF-B, and retinoic acid (125). The transcriptional repressor WT-1 has multiple binding sites in the syndecan-1 promoter and, curiously, enhances transcription (126). Recently, a far upstream enhancer, named FiRE for FGF-inducible response element, was shown
to mediate syndecan-1 induction by FGFs in fibroblasts (112). FiRE is activated by epidermal growth factors (EGFs) and not by FGFs in keratinocytes (127, 128). During wound repair, FiRE is activated only in migrating keratinocytes at the cutaneous wound margin, suggesting that it may reduce syndecan expression under some conditions.

Syndecan expression can also be controlled post-transcriptionally. Syndecan-1 expression is increased 3- and 10-fold without a change in mRNA levels in stratifying keratinocytes (56) and in mesenchymal cells condensing during kidney formation (129), respectively. In contrast, rat heart tissue contains abundant syndecan-3 transcripts, but the PG is hardly detectable (130). Cyclic AMP levels markedly increase cell surface syndecan-1 on thioglycollate-elicited peritoneal macrophages without a change in mRNA levels (131). Moreover, cell surface syndecan-1 is generally decreased on malignant transformation (see 132 for review), but syndecan-1 mRNA levels are unchanged in these cells (133, 134). The mechanisms of this post-transcriptional regulation are largely unknown.

Induction of cell surface syndecan-1 in epithelial cells by Pro-/Arg-rich antimicrobial peptides, TGF-B2, and cAMP agonists such as forskolin and cholera toxin does not increase syndecan-1 mRNA levels (PW Park, G Johnson, T Povsik, M Bernfield, unpublished data). These inductions are blocked by specific inhibitors of protein kinase A, suggesting that the cAMP-PKA signaling pathway can mediate post-transcriptional induction of syndecan expression. How PKA activation contributes to increased levels of cell surface syndecan is not known.

Accelerated shedding can account for a rapid reduction in cell surface HSPGs. Along with activation of protein tyrosine kinases, stimulation of the ERK and JNK/SAPK MAP kinase cascades accelerates syndecan-1 and -4 ectodomain shedding, resulting in their rapid loss from the cell surface (MC Fitzgerald, PW Park, M Bernfield, unpublished data). Glypicans may also be shed from the cell surface, although the mechanism and possible regulation are unknown (108).

SYNDECAN EXPRESSION IS ALTERED BY TISSUE INJURY

After skin injury, syndecan-1 and -4 expression is transiently decreased in keratinocytes migrating into the wound, whereas it is increased in the keratinocytes proliferating at the wound margin and in the fibroblasts (syndecan-4) and endothelial cells (syndecan-1) within the forming granulation tissue (135, 136). This induction is thought to be caused by syndecan-inducing antimicrobial peptides released into the wound by inflammatory cells. Fetal skin, which heals without scarring, shows neither increased syndecan expression nor extensive inflammation (136). In a myocardial infarction model of cardiac injury, an influx of blood-derived macrophages stimulates syndecan-1 expression in endothelial cells and syndecan-4 in cardiomyocytes by the action of a PR-39-like molecule (137). Balloon catheter-induced injury increases syndecan-1 and -4 expression in carotid artery smooth muscle cells (138). Increased syndecan-1 expression in forming granulation tissue correlates with the hepatic fibrosis induced by the parasitic pathogen Schistosoma mansoni (139). Where examined, these
inductions with injury correlate well with syndecan mRNA levels, suggesting that the expression is regulated at the transcriptional level.

CELLULAR EVENTS REGULATED BY CELL SURFACE HEPARAN SULFATE
PROTEOGLYCANS

Cell surface HSPGs bind extracellular proteins and form signaling complexes with receptors (Figure 7). This ligand binding is a means of regulating the occupancy and response of the specific receptor. Additionally, HSPGs immobilize proteins at the cell surface and mediate protein internalization. Thus, ligand binding is followed by various fates. Outcomes seem to depend on whether the ligand is soluble (i.e. growth factor, cytokine) or insoluble (i.e. cell, ECM component, %%%microbe%%%), whether the ligand also interacts with a signaling receptor, and whether the ligand binds to the HS chains on syndecans or glypicans or to their core proteins. Finally, HSPG ectodomains are shed from the cell surface, resulting in soluble PGs that presumably retain all the binding properties of their parent molecules. Because shedding can rapidly reduce HSPGs at the cell surface and the shed ectodomains can compete for ligands with their cell surface counter-parts, shedding provides a means of regulating all HSPG-ligand interactions. Because the soluble ectodomains can interact with any extracellular molecule, they can have activities other than those shown by the cell surface PGs.

EVENTS ASSOCIATED WITH INSOLUBLE LIGANDS

Binding of cell surface HSPGs to insoluble ligands, such as cells and ECM components, immobilizes the PG in the plane of the membrane, enabling the PG to interact with the actin cytoskeleton and form a variety of cell-cell, cell-matrix, or cell-%%%microbe%%% adhesions. The cell surface HSPGs are coreceptors in most of these interactions, generating a second signal upon formation of the signaling complex.

Cell-Cell Adhesion Stabilization of intercellular adhesions. Although HS binds cell adhesion molecules and syndecans localize at adherens junctions (50), direct evidence for cell surface HSPGs mediating physiological cell-cell interactions is meager. Gyrotatory shaking of myeloma cells after stable transfection with syndecan-1 or -4 yields multicellular aggregates owing to binding via the HS chains, but the counterreceptor is unknown (140). The counterreceptor is also unknown for the binding of the syndecan-4 ectodomain core protein to cells described above (45, 46). The HS/heparin interacting protein is on the surface of a variety of epithelial and endothelial cells where it mediates cell-cell and cell-ECM adhesions, but its physiological role is unclear (141, 142). HS binds to L-selectin (143), and monocytes bearing L-selectin may bind to endothelial cell surface HSPGs (144). HS binds the neutrophil integrin Mac-1, but this interaction by itself is too weak to mediate leukocyte-endothelial cell adhesion under flow conditions (145). HS binds the immunoglobulin superfamily adhesion molecules PECAM-1 (146) and N-CAM

(147), whose adhesions are homophilic, and DCC (deleted in colon carcinoma) (148), which is a receptor for the axon chemoattractant and chemorepellant netrin-1 (149). Thus, cell surface HSPG most commonly binds to secondary sites on cell adhesion molecules, apparently to increase the strength or stability of intercellular adhesions.

Maintenance of epithelial phenotype. Syndecan-1 maintains the normal phenotype of simple epithelia by affecting the organization of the actin cytoskeleton and the expression of E-cadherin, the molecule responsible for epithelial intercellular adhesions (80). Syndecan-1 and E-cadherin are simultaneously lost, and the cytoskeleton becomes disorganized when mouse midline palatal epithelial cells undergo an epithelial to mesenchymal transformation (150) and when squamous cell carcinoma cells become poorly differentiated (132). When endogenous expression of syndecan-1 in mouse mammary epithelial cells is suppressed by transfection with antisense cDNA, the cells lose their cuboidal shape and palisaded organization, become fusiform, and gain the ability to invade and migrate within collagen gels and to grow independent of anchorage (80). This dramatic change is accompanied by loss of E-cadherin expression. In a similar fashion, cell surface syndecan-1 is reduced when these cells are manipulated genetically to suppress E-cadherin expression (151). Other epithelia that become fusiform after antibody treatment (152) or oncogene expression (153, 154) also lose E-cadherin. Interestingly, epithelial morphology does not result when syndecan-1 is induced or overexpressed in mesenchymal cells which lack
E-cadherin (113, 116). The mechanism underlying this correlation between syndecan-1 and E-cadherin expression is unknown.

Cell-Extracellular Matrix Adhesion The ECM consists of many large multidomain proteins most of which bind, via discrete domains, to both integrins, a large family of heterodimeric adhesion receptors, and to cell surface HS (see Table 1). These structural proteins may bind to HS at relatively low affinities (i.e. fibronectin Kd of 2 mM). However, the behavior of soluble or isolated ECM molecules likely differs markedly from the in vivo situation where the ECM is an insoluble amalgam with which HSPGs may have multiple, relatively low affinity interactions (36, 155). Syndecans often act as coreceptors in these interactions, modifying cytoskeletal organization and the adhesive phenotype (see 156 for review). The insoluble ECM ligands bind to cell surface HSPGs and cause actin filament reorganization even in the absence of integrin occupancy (6, 157; see 58 for review). Engagement of integrins is followed by activation of a variety of kinase-based signaling systems and the formation of focal adhesions, the multicomponent signaling organelle where actin stress fibers insert into the plasma membrane at sites of close contact (10-15 nm) with the substratum (see 69, 158 for reviews).

Syndecan expression is consistent with a matrix receptor role. Syndecan-1 polarizes to the basolateral surfaces of cultured epithelial cells (49) and of simple epithelial sheets (50) and localizes in early mouse embryos to the initial site of ECM accumulation (159). Syndecan-1 and -3 colocalize with tenascin during tooth (129) and limb (160) development, respectively. Syndecan-1 is expressed on developing B cells only when they are in contact with ECM (161) and it binds B cells to type-I collagen (278). Syndecan-4 and sometimes syndecan-1 (162) localize to focal adhesions (51, 74).

Formation of focal adhesions. Focal adhesions are not formed by HS-deficient CHO cells (163) or by fibroblasts on fibronectin lacking its heparin-binding domain unless a heparin-binding domain peptide is added (164). Antibody-mediated clustering of syndecan-4 at the cell surface induces focal adhesions in cells prespread on substrates coated with the integrin-binding domain of fibronectin (156). Thus, cell surface HSPGs immobilized in the membrane by binding to the heparin-binding domain of fibronectin provide a second signal that is required for formation of stress fibers and maturation of focal adhesions in mesenchymal cells (see 156). This second signal requires the syndecan-4 cytoplasmic domain and presumably involves the interactions with PKCa and PtdIns-4,5-P2 described above (59, 70-74).

Cell spreading. The cytoplasmic domain is not required for the binding and spreading on immobilized thrombospondin or fibronectin of human lymphoblastoid cells transfected with syndecan-1 (52), and neither this domain nor the transmembrane domain are needed for the spreading of the cells transfected with a syndecan-1/glypican-1 chimera on a substrate of monoclonal antibody directed against the syndecan-1 ectodomain (105), or for the formation of actin-containing dendritic processes by antibody-mediated ligation of syndecan-4 on activated B cells (53). The cell spreading likely involves interactions of the syndecan core protein with signaling elements associated with membrane lipid rafts (see 165) or with membrane proteins, as has been shown for the integrins (see 69).

%%%Microbial%%% Pathogenesis The binding of %%%microbial%%% pathogens
to host tissues is a prerequisite for successful %%%infection%%%. Numerous
%%%bacteria%%%, protozoa, and viruses, including both extracellular and intracellular pathogens, bind heparin/HS via a variety of HS-binding proteins (adhesins) (see Table 5). These adhesins are suspected when binding is inhibited by exogenous heparin/HS or the %%%microbe%%% can no
longer colonize cells whose HS expression has been abrogated by chemical or mutagenic methods (see 166 for review). In the absence of other activities, adhesins mediate pathogenesis by binding the %%%microbe%%% to cell surface
HSPGs and enhancing its invasion into the target cell. HS-binding adhesins thus far identified do not show sequence homology but usually contain a binding domain rich in basic residues flanked by hydrophobic domains (166). The binding may be selective for an HS structure or cellular location. For example, only a fully sulfated heparin decasaccharide is capable of inhibiting Dengue virus binding to Vero cells (167), and Plasmodium falciparum binds preferentially to the sinusoidal side of target hepatocytes, suggesting that it binds to the syndecan-1 located at this site. However, for some viruses, the HSPG interaction is suggested to be irrelevant because HS binding is not essential for %%%infection%%% (pseudorabies; 168) or is caused by adaptation of the virus to cell culture conditions (Sindbis; 169, 170).

%%%Microbial%%% Invasion. Cell surface HSPG appears to be used as a coreceptor by intracellular pathogens; the HSPG provides attachment, whereas the other receptor mediates entry of the pathogen into host cells. For example, the initial binding of HSV and other alpha herpes viruses to host cells is mediated by an interaction between viral glycoprotein C and host cell surface HSPG (171). The surface bound virions then fuse with the host cell membrane using interactions between viral glycoproteins B, D, and L and host determinants such as the poliovirus receptor-related protein 1 for internalization (172). Similarly, the interaction between Dengue and foot-and-mouth viruses with cell surface HSPG is proposed to concentrate virus particles at the cell surface for subsequent binding to integrin receptors (173, 174).

Binding of Neisseria gonorrhoeae to cell surface syndecan-4 appears to trigger a signaling cascade that mediates invasion of this pathogen (175). The pathway generates an active phosphatidylcholine-specific phospholipase C, diacylglycerol, acidic sphingomyelinase, and membrane sphingomyelin-derived ceramide, which is essential for the invasion (176). Although the putative second receptor has not yet been identified, in the presence of serum, the %%%bacterium%%% becomes coated with vitronectin and
internalization involves the vitronectin's integrin receptor, avss3.

Syndecan shedding and %%%microbial%%% pathogenesis. Shedding of syndecans from the cell surface appears to accompany host cell invasion by certain pathogens. Invasion by many %%%microbial%%% pathogens requires signaling by protein tyrosine kinases, ceramide, and downstream signaling components such as the MAP kinases (177-179), the same signals that accelerate syndecan ectodomain shedding (48;, ML Fitzgerald, PW Park, M Bernfield, unpublished data). The secreted Pseudomonas aeruginosa virulence factor, LasA, accelerates shedding of syndecans via activation of protein tyrosine kinases (PW Park, M Bernfield, unpublished results), and may augment host cell invasion, a recently described pathogenetic mechanism of this organism (177, 180). The shed soluble syndecan ectodomains can also bind to and inhibit the activity of proline- and arginine-rich antimicrobial peptides, suggesting that the shed ectodomains may be involved in pathogenesis (PW Park, M Bernfield, unpublished data).

EVENTS ASSOCIATED WITH SOLUBLE LIGANDS

Cell surface HS sequesters secreted soluble ligands and modulates their activity. As coreceptors, HSPGs modulate ligand-receptor encounters that can activate and inhibit cell proliferation, motility, and differentiation. As receptors, HSPGs regulate internalization and clearance of their ligands via both clathrin-coated pits and membrane lipid rafts associated with caveolae.

Growth Factor, Cytokine, and Chemokine Action Cell surface HSPGs are implicated in cell signaling from a large variety of soluble effectors (see Table 1). Ligand binding to cell surface HS yields a sufficiently high local ligand concentration to activate signaling receptors. In most cases, this binding facilitates but is not required for ligand-receptor interaction and signaling. Initial studies with FGFs and their receptor tyrosine kinases documented this coreceptor role for HSPGs and suggested models in which HS promotes ligand dimerization, leading to receptor dimerization and stimulation of kinase activity (181). It is now evident

that many receptor classes, including receptor serine/threonine kinases and seven pass transmembrane receptors, are modulated by HSPGs, using several distinct mechanisms.

Fibroblast Growth Factors and Other Growth Factors with Tyrosine Kinase Receptors. The FGFs are a large family of monomeric heparin-binding growth factors that function during development, would repair, angiogenesis, and atherosclerosis, among other processes. Since the observations that cell surface HS was involved in the binding (182) and activity of FGF-2 (183), modulation of FGF interactions with FGF-Rs by HS has been extensively studied as the prototype growth factor-receptor tyrosine kinase interaction (see 181 for review).

The FGFs are small globular proteins with separate binding regions for HS, the FGF-Rs, and possibly for forming dimers. Heparin or HS is not required for receptor binding but enables the formation of a high-affinity complex that potentiates receptor signaling at low growth factor concentrations (184, 185). FGF-2 binds to a specific pentasaccharide sequence in heparin or HS containing an essential IdoA(2S) residue and no 6-0-S groups (186), but a decasaccharide or larger of an HSD containing a 6-0-S group is needed for HS to dimerize the growth factor (187) and activate the receptor (280). Activity results from bringing the kinase domains into close proximity potentiating the phosphorylation of one receptor kinase by the other (see 54 for review). The HSDs also bind to FGF-R1, the FGF-2 receptor, in a manner that the 6-0-S group may generate a
template for ligand docking to the receptor (36, 188). This model is consistent with the crystal structure of FGF-oligosaccharide and molecular modeling of the HS-FGF-2-FGFR-1 complex (189). Heparin and other sulfated
GAGs are able to activate FGF-R4 but not FGF-R1 in an FGF-independent manner, suggesting a direct role for HSPGs in receptor activation (190). Potentiation of FGF-2 activity has been shown with cell surface syndecan-1, -2, and -4, as well as glypican-1 (106). However, in some studies, cell surface and soluble HSPGs behave differently in potentiating FGF-2 mitogenicity (see 192 for discussion). Despite extensive study, there is still much to be learned about the HS-induced potentiation of FGF activity.

Syndecan-1 HS chains purified from epithelial cells and from fibroblasts differ in GAG structure as well as their ability to interact with ligands such as FGF-2 and type-I collagen (29). Recently, distinct binding sites for hepatocyte growth factor (also known as %%%scatter%%% %%%factor%%%), FGF-1, and FGF-2 were identified in HS from ductal epithelial, myoepithelial, stromal fibroblast, and malignant mammary epithelial cells. The sites show different binding kinetics, affinities, and ability to stimulate signaling and mitogenesis (191).

In addition to the FGF family, the EGF and platelet-derived growth factor (including vascular endothelial growth factor) families, as well as the large proteaselike hepatocyte growth factor, use single-transmembrane receptor tyrosine kinases that are activated by dimerization. In these instances (e.g. HB-EGF, amphiregulin, betacellulin, platelet-derived growth factor AA, vascular endothelial growth factor 165 and 189), binding to cell surface HS is thought to potentiate receptor dimerization. However, the mechanism used by these growth factors, as well as by some FGF family members (e.g. FGF-1, -7), differs from that proposed for FGF-2. For example, hepatocyte growth factor, a potent mitogenic and motogenic agent, is a disulfide-linked heterodimer that binds heparin more tightly than FGF and whose activity is markedly enhanced by HS but apparently does not require HS to bind to its receptor, c-met. (193).

Other Growth Factors and Cytokines and Their Receptors. TGF-ss1 and-ss2 bind heparin; TGF-ss3 does not (194). These growth factors are disulfide-linked dimers that signal via two transmembrane serine/threonine kinases. Growth factor interaction with HS neither activates nor inhibits receptor signaling but protects the growth factors from inactivation by a2-macroglobulin (194). Receptors for the cytokines that bind heparin (195) e.g. interleukin (IL)-2, IL-3, granulocyte-macrophage-colony stimulating factor differ from receptor tyrosine kinases by not containing a kinase domain; rather, their cytoplasmic do-mains associate with Janus kinases (JAKS). The way in which interaction with HS modulates cytokine activity is unknown.

Seven Pass Transmembrane Receptors. All C-C and CXC chemokines (e.g. IL-8, Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES), interferon-g inducible protein-10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1)) oligomerize on interaction with cell surface HS, enhancing activation of their seven pass transmembrane receptors (196). The activity of many members of the Wnt family of morphogens, including Wnt-1 and its Drosophila ortholog, Wingless (Wg), is markedly enhanced by cell surface HS. These signal through members of the Frizzled family of seven pass transmembrane receptors. Unlike the kinase receptors, these receptors are not thought to be activated by dimerization, and the mechanism of cell surface HS action is unknown.

Developmental Antagonists. The action of some developmental antagonists of morphoregulatory molecules and growth factors may be augmented by binding heparin/HS, e.g. the inhibitory action of chordin on bone morphogenetic protein 4 (197), follistatin on activin (198), the 60-kD binding protein on TGF-ss (199), agouti signaling protein on a-melanocyte stimulating hormone (a-MSH) (O Reizes, M Bernfield, unpublished data), and frizzled-related peptides on Wnt-1 and on Wg (200), and sprouty on branchless (Bnl, FGF homolog) in Drosophila melanogaster (201). Interestingly, each of these otherwise dissimilar antagonists is a secreted, cysteine-rich heparin-binding protein.

Internalization and Clearance Soluble ligands bound to cell surface HSPGs can function at the cell surface, as exemplified by AT III and lipoprotein lipase. These ligands can be internalized along with the HSPG as part of normal turnover and can be recycled; entry into lysosomes is needed to degrade the HS chains (94). However, there are a variety of putative uptake receptors, making it unclear to what extent ligand uptake represents internalization by cell surface HSPG. For example, antithrombin III uptake can be mediated via cell surface HSPG, the serpin-enzyme complex
(SEC) (202), the low-density lipoprotein (LDL)-receptor-related protein (LRP) (203), and the very-low-density lipoprotein (VLDL) receptor (204), making the contribution of HSPG to the residence time of antithrombin III at the cell surface difficult to assess.

HSPGs are also implicated in uptake of the follistatin/activin complex, FGF-2, vitronectin, and thrombospondin. Follistatin binds activin, and vitronectin binds a variety of ligands, and these complexes are cleared by HSPGs via the clathrin-coated pit-lysosomal pathway (99). FGF-2 can be internalized on both syndecans and glypicans via caveolae through an FGF receptor-independent mechanism (205).

Lipoprotein Metabolism. The metabolism of atherogenic lipoproteins clearly involves the classical LDL receptor (9), but heparin/HS has long been known to be involved in LDL-receptor-independent pathways. These pathways account for a substantial proportion of hepatic uptake and arterial accumulation of lipid (206). Binding of lipoprotein lipase to cell surface HS is key to these pathways. Lipoprotein lipase, is produced primarily by adipocytes, as an inactive monomer that binds HS much less well than the dimer (207). Dimeric lipoprotein lipase binds at high affinity (Kd of 0.3 nM) (207) to the HS on the surface of endothelial cells and hepatocytes where it degrades neutral fat in chylomicrons and VLDL, as well as binds apolipoproteins B and E (apoB and apoE) for uptake and degradation (208). Lipoprotein lipase also binds LDL-receptor-related protein at a domain that overlaps with its HS-binding site (209). Recent studies indicate that syndecans act as internalization receptors for lipoprotein lipase and its bound ligands via a a non-coated pit pathway leading to lysosomal degradation (110, 208, and 210). This route may be quantitatively more important than the LDL-receptor-related protein pathway
(211).

SHEDDING FROM THE CELL SURFACE

Of membrane-anchored proteins, ca.1[percent] undergo regulated proteolytic
cleavage near the plasma membrane, resulting in release of their ectodomains as soluble intercellular regulators in a process known as shedding (reviewed in 212, 213). These functionally diverse proteins include cell adhesion molecules, cytokines, growth factors and their receptors, enzymes, and the syndecans. Shedding instantly converts membrane-anchored molecules into soluble effectors. Shedding of receptors or coreceptors, like the syndecans, can produce agonists or antagonists that regulate their ligand's activities, render cells less responsive to their ligands, and potentially generate an active fragment that remains membrane-associated or becomes intracellular.

The intact ectodomains of each mammalian syndecan and the single Drosophila syndecan are constitutively shed into the conditioned media of cultured cells (47, 61) as part of cell surface HSPG turnover (162). However, syndecan shedding can also be accelerated in a highly regulated manner (48; ML Fitzgerald, in preparation) (see Figure 8). Shedding of syndecan-1 and -4 from epithelial or endothelial cells is accelerated by direct proteolytic cleavage (thrombin, plasmin), by cellular stress (mechanical, heat shock, hyperosmolarity) acting through the Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) pathway (214), and by activation of several other intracellular signaling pathways. These include phorbol ester stimulation of PKC (48), pervanadate inhibition of protein

tyrosine phosphatases (65), and EGF and thrombin receptor activation of the
extracellular signal-regulated protein kinase (ERK) pathway (48; ML Fitzgerald, PW Park, M Bernfield, unpublished data), and insulin receptor activation of via PI-3 kinase (adipocytes only) (P Bickel, O Goldberger, H Lodish, M Bernfield, unpublished data). All accelerated shedding involves protein tyrosine kinase activity (see Figure 8). Secreted products of certain %%%bacterial%%% pathogens also accelerate this shedding (PW Park, M
Bernfield, unpublished data). The syndecan-1 ectodomain is shed via cleavage of the core protein within 15 amino acids of the plasma membrane by a cell surface-associated (not soluble) proteinase(s) (Z Wang, M Bernfield, unpublished data). Ectodomain shedding is inhibited by peptide hydroxamate chelators of zinc ions (215), and tissue inhibitor of metalloproteinase 3, but not tissue inhibitor of metalloproteinase 1 or 2 (216). These findings are consistent with the proteinase being a member of the ADAM (a disintegrin and metalloproteinase) family of cell surface proteinases (217, 218). Thus, multiple extracellular agonists acting through distinct signaling pathways converge to activate a cell surface metalloproteinase(s) that causes the shedding of syndecan ectodomains.

IN VIVO ACTIVITIES OF CELL SURFACE PROTEOGLYCANS

Evidence presented above makes clear that cell surface HS interacts with multiple ligand and receptors and participates in the regulation of diverse processes. However, these activities must be understood in whole organisms to appreciate how they are integrated and how they relate to normal physiology and to disease. Recent transgenic and gene deletion approaches in mice and genetic screens in D melanogaster are providing surprising phenotypes that have major implications for understanding cell surface HS functions in vivo.

DROSOPHILA HEPARAN SULFATE PROTEOGLYCANS

Cell surface HS is initially expressed in the embryo at cellularization, is extensively expressed in the ventral epithelium, the site of initial gastrulation, and then becomes widespread in the mesoderm, ectoderm, and endoderm (J Lincecum, M Bernfield, unpublished data). D. melanogaster appears to have only a single syndecan gene (61). During embryogenesis, D syndecan transcripts are detected in the ventral furrow, the ventral nerve cord, the abdominal and thoracic segments, the epidermis, and the differentiating CNS (219). By late embryogenesis (stage 16), D syndecan is expressed in the lymph glands, the peripheral and CNS, (Berkeley Drosophila Genome Project, as cited in Reference 219), and the basal surfaces of the gut epithelium (61).

The Drosophila glypican gene dally was identified in a genetic screen to obtain mutants affecting cell division patterning in the CNS, implicating glypicans in the control of cell division during development (89). dally expression in the early embryo has not been extensively characterized. However, by segmentation (stage 9), dally transcripts are found in a segmentally repeated pattern (X Lin, N Perrimon, unpublished data).

Mutants of Heparan Sulfate Proteoglycan Biosynthesis The formation of specific structures during fly embryogenesis involves stable concentration gradients of soluble factors (morphogens) that dictate different developmental outcomes at different concentrations. Recent genetic screens investigating signaling by the secreted morphogens Spaetzle, Wingless, and Hedgehog have identified mutations in putative HS biosynthetic enzymes (220-222). The mutants have also provided genetic evidence that HS is required for FGF-R signaling during embryogenesis (X Lin, EM Buff, N Perrimon, AM Michelson, unpublished data). Moreover, a mutant glypican causes abnormalities in the activity of another secreted morphogen, decapentaplegic (Dpp) (223). Although the enzymes must still be characterized biochemically, these results provide evidence for the physiologic role of HSPGs during development as modulators of signaling molecules, as activators of proteolysis and potentially as initiators of morphogen gradients (Table 6).

Dorsal-Ventral Axis Formation. The dorsal-ventral axis of the Drosophila embryo is established by the action of several genes that localize the transcription factor Dorsal. One proposal is that localized Pipe activity in the ovarian follicular epithelium is required for ventral-specific proteolytic activation of Spaetzle, the Toll ligand, which then produces a gradient of activated Toll, which, finally, induces the nuclear localization of Dorsal (224). The proteolysis involves the serine proteinases Snake, Easter, and Gastrulation Defective. The pipe gene was recently found to encode two isoforms of a vertebrate HS 2-O-sulfotransferase homolog (220), although their enzymatic activities have not been characterized. Therefore, 2-O-sulfation of IdoA residues in HS is likely required for proteolytic activation and ventral localization of Spaetzle. Because serpins can regulate the production of active Spaetzle (225), an HSPG could activate the proteolytic cascade by protecting the proteinases from inhibition by serpins, an activity shown by syndecan ectodomains in inflammatory fluids (226) (see left panel, Figure 9). A relationship to inflammation is consistent with the newly recognized role of the Toll homolog as a trigger of the vertebrate innate immune response (227) and of Dorsal as an analog of NF-kB, the transcription factor that is active in inflammation.

Wingless Signaling and Segmentation. Wingless (Wg) is a secreted heparin-binding morphogen required for patterning of the embryonic parasegments and for maintenance of engrailed expression in adjacent cells (see 228 for review). Wg is homologous to Wnt-1, the prototype member of a
large family of vertebrate heparin-binding differentiation factors. Screens for genes required for Wg activity identified sugarless (sgl), a homolog of bovine UDP-glucose dehydrogenase (221, 229, 230), and a homolog of a mammalian N-deacetylase/N-sulfotransferase, named sulfateless (sfl) (X Lin,
N Perrimon, unpublished data). The sgl and sfl null embryos exhibit a cuticle phenotype similar to that of wg-mutants, indicating that the Wg signal is not properly transmitted in the absence of GAG chains or of N-sulfation, consistent with cell culture findings that cell surface HS is required for efficient transduction of the Wg signal (reviewed in 231). Heparinase injection into flies generates sgl phenocopies, and HS injection rescues sgl mutants, suggesting that sgl functions non-cell autonomously (229). The dally expression pattern is consistent with it being the HSPG involved in Wg signaling in the parasegments.

Hedgehog Diffusion. Hedgehog (Hh) is a secreted heparin-binding morphogen that exerts both short- and long-range effects in fly embryos. hedgehog and its vertebrate homologs have a variety of developmental functions. Hedgehog appears to act by binding to Patched, releasing its inhibition of Smoothened, both transmembrane proteins. Mutations in the human homolog of patched are widespread in basal cell carcinomas (reviewed in 232). A screen for mutants associated with segment polarity defects demonstrated that tout-velu (ttv; French for all-hairy) is required for Hh diffusion (222). tout-velu encodes the Drosophila homolog of the putative human tumor suppressor genes EXT1 and EXT2 (222), both of which may encode
the HS polymerase enzyme (17, 233). Sequestering of Hh by binding to Patched can account for the short-range effects of Hh. tout velu suggests that HSPGs affect long-range Hh diffusion by activating Hh release or transport, possibly by a shed soluble HSPG ectodomain.

Signaling via FGF-Rs. The sgl and sfl mutant embryos also have phenoypes similar to those lacking the functions of two Drosophila FGF-Rs, Heartless (Htl) and Breathless (Btl) (X Lin, EM Buff, N Perrimon, AM Michelson, unpublished data). Htl is required for the dorsolateral migation of early embryonic mesoderm cells following gastrulation and for specification of certain cardiac and muscle cell fates, while Btl and Branchless (Bnl), the Btl ligand, are required for the migration and determination of certain tracheal cells (234, 235). Importantly, the defects in mesodermal and tracheal cell migration in the HS mutants are partially rescued by a constitutively activated Htl and show dosage-sensitive genetic interactions with Htl and with Bnl, consistent with a coreceptor role for HS. Dsyndecan is likely involved in these pathways because of its specific expression in both early mesoderm and tracheal cells.

Dpp and Patterning. The fly homolog of bone morphogenetic proteins, DPP is a morphogen that controls axial patterning of the wing and leg. Mutations in dally enhance Dpp mutant phenotypes in the eye, antenna, and genitalia but suppress Dpp defects in the wing imaginal disks, possibly by affecting wg signaling (223). Ectopic expression of dally can alter the patterning activity of Dpp, suggesting a role for dally in modulating Dpp signaling strength (230). The sgl mutations also suppress phenotypes resulting from ectopic overexpression of Dpp in the wing imaginal disk. Taken together, these results suggest that dally acts as a cell surface coreceptor for Dpp.

GENETIC LESIONS IN MOUSE HEPARAN SULFATE PROTEOGLYCANS

Several mammalian morphoregulatory molecules, including those involved in establishing the vertebrate basic body plan, bind heparin/heparan sulfate (see Table 1). However, mice with a null mutation in syndecan-1, the sole cell surface HSPG known to be expressed during early mouse development (90,

111), show no defects in morphogenesis. This normal development, presumably enabled by compensation by other HSPG structural genes, suggests that mutations of these genes in mice, unlike in flies, may not elucidate their developmental roles. More informative might be mutations in genes for HS biosynthetic enzymes that generate specific HS structures (236), or mutations that yield excessive soluble ectodomains which, via their HS chains, inhibit the interactions of cell surface HSPGs.

Targeted Disruption of the Syndecan-1 Gene Syndecan-1 is the earliest cell surface HSPG to appear during mouse embryogenesis (90, 111). Its subsequent expression coincides with the cells fated to become the embryo proper, and it is tightly regulated during the epithelial-mesenchymal interactions of organogenesis, and predominates in adult epithelia and plasma cells. To assess the function of syndecan-1 in vivo, the syndecan-1 gene was disrupted by homologous recombination in mouse embryonic stem cells. Surprisingly, Synd1 -/- mice are viable, develop normally, are fertile, and phenotypically indistinguishable on either BALB/c or C57BL/6 backgrounds from wild-type littermates by histology of tissues and cytology and chemistry of blood. Thus far, the sole abnormality detected in the Synd1 -/- mouse is defective repair of skin (H Gibson, MT Hinkes, M Bernfield, unpublished data) and corneal wounds (MA Stepp, M. Bernfield, unpublished data). At both sites, lack of syndecan-1 prevents keratinocytes (or keratocytes) migrating into the wound from restoring their stable cell-cell and cell-matrix contacts at a normal rate. The result is a marked delay in reconstitution of the normal epithelium. Thus, the essential function of syndecan-1 appears to be for normal epithelial behavior during wound repair.

Renal, Ocular, and Skeletal-Defect Syndrome Mice homozygous for a gene trap mutation that disrupts the gene encoding HS 2-O-sulfotransferase die in the neonatal period exhibiting a novel syndrome of bilateral renal agenesis, bilateral coloboma of the iris, skeletal fusions, and ectopic ossification (236). Kidney development in these mutants shows defective condensation of the metanephric mesenchyme and failure of the ureteric bud to initiate branching. This enzyme presumably has the same activity as the product of the Drosophila pipe gene, but mice show at least two HS 2-O-sulfotransferase isoforms (283). The morphogenetic abnormalities likely arise from a tissue-specific deficiency of 2-O-sulfation of IdOA residues in HS, leading to compromised interactions between the growth factors responsible for this organogenesis and their cognate receptors.

Interactions of the Soluble Syndecan-1 Ectodomain To evaluate the functions of syndecan-1 during skin wound repair, wounds were studied in mice overexpressing syndecan-1 in the skin under the influence of the cytomegalovirus promoter/enhancer. Compared with wild-type mice, wound closure, reepithelialization, granulation tissue formation, and remodeling were delayed [similar]5 days in mice that overexpress syndecan-1 (V Kainulainen, O Reizen, W Avery, J Madri, M Bernfield, unpublished data). Wounding of both wild-type and overexpressing mouse skin caused shedding of the soluble syndecan-1 ectodomain into wound fluids, but the shedding was markedly enhanced and prolonged in wounds from overexpressing mice. These wounds showed substantially reduced cell proliferation rates for keratinocytes at wound edges and for granulation tissue cells, and accumulated fluids containing increased elastolytic activity. The reduced cell proliferation rates and enhanced proteolytic activity were caused by excess soluble syndecan-1 ectodomain that acts as a dominant negative inhibitor of cell proliferation and protects the neutrophil elastase from inhibition by serpins in the wound fluid (226, 245) (see Figure 9).

HUMAN DISEASE

Patients with mutations in putative HS polymerase genes and in the glypican-3 gene show bone and generalized somatic overgrowth, respectively, both with variable severity and a slight tendency for neoplasia (17, 233, 239). The pathogenesis of these syndromes is unknown, but cell surface HSPGs interact with a variety of ligands involved in growth control (see Table 1) and might be weak tumor supressors. The soluble syndecan ectodomains that appear in injured tissues (226) modulate the accompanying inflammatory response, suggesting that they are host defense molecules. This newly recognized role may contribute to the mechanisms underlying innate immunity.

Hereditary Multiple Exostoses Hereditary multiple exostoses are autosomal dominantly inherited disorders characterized by development of multiple exostoses, benign tumors derived from the growth plate of endochondral bones, which occasionally undergo malignant transformation to chondrosarcomas and more rarely to osteosarcomas (237). The cause is mutations in the EXT1 or EXT2 genes that encode the HS polymerase enzyme (17, 233), the homolog of the tout velou gene in D. melanogaster that is responsible for facilitating diffusion of the Hh morphogen (222). Mutations in either unlinked gene cause exostoses, suggesting that the enzymes cannot substitute for each other (17). The genes reportedly can act as tumor supressors (238).

Simpson-Golabi-Behmel Syndrome This rare X-linked syndrome associated with mutations in the glypican-3 gene (239) is characterized by both pre-and postnatal overgrowth, a distinct facial appearance, macroglossia, a predisposition for embryonal tumors, and a variable spectrum of anomalies (240). These include cleft palate, congenital heart disease, umbilical hernia, renal defects, vertebral and rib defects, polydactyly, imperforate anus, and genito-urinary anomalies. Perinatal and infant mortality is high. In at least one family, the syndrome appears to be caused by a combined defect in the closely linked glypican-3 and glypican-4 genes on Xq26 (241). Mentation is usually normal. The mechanism of somatic overgrowth is wholly unclear, as is the basis for the malformations and the increased risk of neoplasia.

Inflammation and Tissue Repair A variety of experimental injuries are accompanied by transient induction of syndecan-1 and-4 in the cells of the wounded tissue (116, 135, 137, 138). Cellular stress, proteinases, and growth factors released at the site of injury accelerate the shedding of syndecan ectodomains. The syndecan-1 and-4 ectodomains are found in acute dermal wound fluids of patients (48, 107) and in tracheal fluids of infants whose lungs have been injured by mechanical ventilation. On the other hand, soluble syndecan ectodomains are not in normal human plasma (48). The syndecan-1 ectodomain is in the plasma of myeloma patients with a high tumor burden, and its level may be of prognostic value in this plasma cell malignancy (279).

The shed syndecan-1 and -4 ectodomains maintain growth factor and proteolytic balance at the wound site (226, 245). Major growth factors involved in skin wound repair are HB-EGF and FGF-2 (242). The soluble syndecan-1 ectodomains inhibit both HB-EGF (HM Wang, M Klogsbrun, M Bernfield, unpublished data) and heparin-mediated FGF-2 mitogenicity (245), consistent with studies indicating that the soluble ectodomains inhibit cell proliferation (243, 244). Inhibition of FGF-2 activity is via the UMD of the HS chains (245). However, enzymes like neutrophil heparanase, which is secreted into wound fluids, degrade the UMD, abolishing the inhibition and liberating HSD that markedly stimulate FGF-2 mitogenicity. Indeed, physiologically significant concentrations of mitogenically active HS fragments that resemble HSD are in human acute wound fluid (245). Thus, physiological degradation converts the soluble ectodomain from an inhibitor to a potent activator of FGF-2 mitogenicity needed for normal wound repair.

A proteinase-antiproteinase imbalance plays a role in mediating inflammation-induced injury. The major inflammation-associated proteinases are neutrophil-derived elastase and cathepsin G, enzymes that bind heparin (246) and the syndecan-1 ectodomain (226). Like heparin, the soluble ectodomain reduces the affinity of these proteinases for their physiological inhibitors, the plasma-derived serpins a 1-antiproteinase and a 1-antichymotrypsin, which also are in wound fluids (226). The soluble ectodomains protect the proteinases from these inhibitors, thus increasing proteolytic activity and tissue injury (see left panel, Figure 9). This modulation varies with the nature of the proteinase inhibitors. In tracheal inflammatory fluids, the major protease inhibitors are derived from the respiratory tract, specifically the serpin squamous cell carcinoma antigen 2, which acts on cathepsin G (247), and the secretory leukoprotease inhibitor, which acts on elastase (248). The syndecan ectodomains in these fluids protect cathepsin G from inhibition by the serpin, as in wound fluid. However, because secretory leukoprotease inhibitor has a different mechanism of action, the ectodomains reduce elastolytic activity (see right panel, Figure 9) (V Kainulainen, ML Fitzgerald, M Bernfield, unpublished data).

The action of the ectodomains during tissue injury is transient. Tissue repair is accompanied by accumulation of fibrotic deposits of interstitial ECM components, including fibrillar collagens, fibronectin, and tenascin. These ECM deposits bind both the HSD and soluble syndecan ectodomains, thus limiting their activity and effectively terminating their influence (5, 102).

SUMMARY AND PERSPECTIVES

Because HS chains are very similar among organisms as diverse as insects, mollusks, and mammals, the conservation of HS binding by extracellular proteins suggests that their association with HS is ancient and

functionally relevant. Indeed, proteins whose functions depend on interactions with HS have likely coevolved with these HS chains. Extracellular HS-binding proteins so far identified have roles in morphogenesis, tissue repair, host defense, or energy metabolism, each a process that is critical to survival of metazoan organisms.

The repertoire of HS biosynthetic enzymes generates HS chains with highly variable fine structure. Cells modify HS structures during development and certain pathological processes. Specific saccharide sequences are involved in interactions with certain proteins. However, the HS code likely has substantial degeneracy, as should become evident with the application of new sequencing techniques and the phenotypic characterization of mutations in HS biosynthetic enzymes.

Most of the HS at the cell surface is linked to members of two core protein families, the transmembrane syndecans and the membrane lipid-anchored glypicans. These proteins behave as products of developmental genes: conserved in evolution and active at multiple sites and times during development and again during pathophysiologic processes. Although few family-specific functions are currently known, because these proteins differ in structure, mode of association with the plasma membrane, and expression pattern, they likely have distinct interactions and roles.

These cell surface HSPGs modulate the actions of a wide variety of HS-binding proteins. They act as coreceptors with signaling receptors and directly as endocytosis receptors. As coreceptors, they potentiate the action of low concentrations of ligands by enhancing the formation of ligand-receptor complexes. The actin cytoskeleton is engaged when the HSPGs
interact with insoluble ligands, as during cell-cell or cell-ECM adhesion or %%%microbial%%% invasion. Intracellular signaling or endocytosis is augmented when the HSPGs interact with soluble ligands. Modulation of ligand action by HSPGs results from several distinct mechanisms, some of which will be subject to pharmacologic manipulation.

The extracellular domains of these HSPGs can be shed from the cell surface in a regulated manner. Now soluble effectors, these PGs can inhibit interactions at cell surfaces and affect the activity of other mediators. Shedding is accelerated by tissue injury, and soluble ectodomains accumulate in inflammatory fluids. The expression and function of these HSPGs should be assessed in inflammatory responses to injury, including atherosclerosis, hepatic cirrhosis, pulmonary fibrosis, tumor invasion, and metastasis.

Mutants of HS biosynthetic enzymes and of syndecan and glypican structural genes in flies, mice, and humans confirm that HSPGs function during morphogenesis and tissue repair. Based on the mutant phenotypes, many additional functional interactions of these HSPGs will likely be described, especially within integrative systems (e.g. nervous, endocrine, and innate immune systems). Deciphering their physiologic role will establish why cell surface HSPGs and HS-binding proteins have been so successful during metazoan evolution.

Added material

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TABLE 1 Proteins of cellular microenvironment bound by heparin/heparan sulfate (partial list)(FNa)

FOOTNOTES

a Summarized from References 8, 9, 58 and Reizes, PW Park, M Bernfield and
unpublished observations. Abbreviations: BMP, bone morphogenetic protein; FGF, fibroblast growth; EGF, epidermal growth factor; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor; IL, interleukin; GM-CSF, granulocyte-monocyte colony stimulating factor; TNF, tumor necrosis factor; N-CAM, neural cell adhesion molecule; PECAM, platelet-endothelial cell adhesion molecule; Bac, bactinecin.

b Cell adhesion molecules are also involved in morphogenesis.

TABLE 2 Recent publications on general and topical aspects of cell surface heparan sulfate proteoglycans

TABLE 3 Syndecan family(FNa)

FOOTNOTE

a Summarized from References 8, 61, 111. CNS, Central nervous system.

TABLE 4 Glypican family(FNa)

FOOTNOTE

a Summarized from References 90, 201, 241, 252, 255, 283. CNS, Central nervous system.

TABLE 5 Mibrobial pathogens that bind to cell surface heparan sulfate proteoglycans

TABLE 6 Mutations in proteoglycan biosynthesis affect Drosophila morphogenesis(FNa)

FOOTNOTE

a Summarized from References 220, 222, 223, 231, 275 and X Lin, N Perriman,
unpublished data.

Figure 1 Scheme of heparan sulfate biosynthesis. The biosynthetic enzymes act sequentially; the product of each reaction is the substrate for the next. The reactions presumably do not go to completion, yielding individual chains whose sequence is likely distinct from all other chains (13, 276). The size of the HS chains depicted here is arbitrary. Highly sulfated domains (HSD; left side of chain depicted here) alternate with relatively unmodified domains (UMD). The HSD are readily distinguished from
the UMD by their susceptibility to HNO2 at pH 1.5 and to heparin lyase I (heparinase), whereas the UMD are digested by heparin lyase III (heparitinase) (9). See text for details.

Figure 2 Schematic depiction of cell surface heparan sulfate (HS) proteoglycans. Syndecans are transmembrane proteins that bear HS chains distal from the plasma membrane (6). Some syndecans also contain ChS chains, which, by homology to syndecan-1, are near the membrane (43). Based
on their high proline content, the syndecan ectodomains are likely extended proteins. Glypicans are covalently linked to a phosphatidyl inositol in the outer leaflet of the plasma membrane. The HS chains are located on a likely extended protein domain near the plasma membrane (7). The glypican ectodomains are presumably compact and globular proteins due to their characteristic 14 conserved cysteine residues. The disulfide bonds shown here are arbitrary; the actual number of such linkages is unknown. See text for details.

Figure 3 Diagrams showing the derived core protein domain organization, locations of putative GAG attachment sites, dendrogram and aligned sequences of human syndecan-1 (SDC1), SDC2, and SDC4 rat syndecan-3
(Synd3; the human syndecan-3 sequence is not known), and Drosophila syndecan (D-Sdc). The proteins are aligned at the signal peptides and the transmembrane domains, leaving gaps in the ectodomains. The GAG attachment
sites represent ser-gly dipeptides that are preceded and followed by acidic residues. Locations of the three invariant cytoplasmic domain tyrosines and single invariant transmembrane domain tyrosine are shown. The dendrogram, provided by Pileup, which predicts genetic distances between sequences, suggests that the D-Sdc gene is derived from a common ancestor of the four
mammalian syndecan genes and that SDC1 and Synd3 form one subfamily and

SDC2 and SDC4 form another. These genes are distributed throughout the mammalian genome (see Table 3) and apparently arose by two gene duplications after the divergence of the insect and vertebrate lineages (modified from Reference 61).

Figure 4 Hypothetical models for interactions of the syndecan cytoplasmic domains. (Left) Syndecan-3 as a potential signaling receptor. Syndecans within the plasma membrane are shown as dimers, although the state of oligomerization in vivo is not known. The cytoplasmic domain of syndecan-3 binds the tyrosine kinases c-Src and c-Fyn (not shown), as well as cortactin (p80/85) and tubulin (brown symbols) in crude brain extracts. Binding of heparin-binding--growth-associated molecule (HB-GAM; also known
as pleiotropin and as midkine) to syndecan-3 in neuroblastoma cells results in neurite outgrowth and increased phosphorylation of c-Src and cortactin (68). (Right) Syndecan interactions with actin-binding proteins and F-actin. The EFYA motif of the conserved C2 region of the cytoplasmic domain on all syndecans interacts with the PDZ domains of the multidomain proteins CASK/LIN-2 and syntenin (83, 84). CASK/LIN-2 binds the actin-binding protein 4.1 and thus might link syndecans to the actin cytoskeleton (blue symbols) (84). Tyrosine residues on the cytoplasmic domain of all mammalian syndecans can be phosphorylated in vivo, potentially regulating the association of syndecans with scaffolding molecules like syntenin and CASK/LIN-2. GUK, guanylate kinase; CAMK, calcium/calmodulin- dependent protein kinase; SH3, Src homology 3.

Figure 5 Hypothetical models of syndecan-4 cytoplasmic domain phosphorylation within focal adhesions. Syndecan-4 is shown as a dimer as described in the legend to Figure 4. (A) Binding of phosphatidylinositol-4,5-bisphosphate (PtdIP2) to the V region of the cytoplasmic domain, presumably to positively charged lysine groups adjacent to the unphosphorylated serine in the C1 region, facilitates dimerization of the proteoglycan (59, 71). (B) The dimerized cytoplasmic domain binds and activates the catalytic domain of PKCa (70). (C) Phosphorylation of the cytoplasmic domain presumably by PKCa reduces its affinity for PtdIP2 and the proteoglycan dimer dissociates (87). (D) Phosphatases, including phosphatase activated by fibroblast growth factor-2 (FGF-2) (67), return the cytoplasmic domains to their unphosphorylated steady-state form. This effect of the growth factor would facilitate syndecan-4 oligomerization.

Figure 6 Diagrams showing the derived core protein domain organization, locations of putative GAG attachment sites, dendrogram, and aligned sequences of human glypican-1 through -6 and dally, the Drosophila glypican homolog. The proteins are aligned at the signal sequence and show the 14 conserved cysteines that are spaced similarly among all glypicans. The GAG attachment sites and dendrogram are as in the legend to Figure 3. The dendrogram suggests that glypican-3 and -5 and glypican-4 and -6 form subfamilies, consistent with the possible tandem clustering of these genes on Xq26 and 13q31-32, respectively (see Table 4). (After References 90, 249; S Saunders, personal communication).

Figure 7 Functions of cell surface heparan sulfate proteoglycans. For convenience, only syndecans are depicted here, but, except as noted, glypicans probably function similarly. The proposed functions are the following. (A) Coreceptors for insoluble ligands e.g. extracellular matrix (ECM) molecules, cells, %%%microbes%%% that immobilize the receptor complex in the plane of the membrane causing it to associate with actin microfilaments. Glypicans do not likely subsume this function. (B) Coreceptors for soluble ligands (e.g. growth factors, chemokines, cytokines) that form part of a signaling complex with their signal transducing receptors. (C) Internalization receptors for soluble ligands (e.g. enzymes, serpins) that present ligands at the cell surface and take ligands into cells via either coated pits or caveolae for degradation, recycling, or transcytosis. (D) Soluble paracrine effectors produced by shedding of the heparan sulfate proteoglycan (HSPG) ectodomains from the cell surface. Shedding instantly changes the function of the HSPG and can reduce the level of cell surface HSPGs. Syndecan shedding leaves a potentially interactive peptide containing transmembrane and cytoplasmic domains remaining with the cell. See text for details.

Figure 8 Multiple physiological agonists acting through distinct signaling pathways accelerate the shedding of syndecan ectodomains from the
cell surface. The ectodomains of mammalian and Drosophila syndecans can be shed intact by proteolytic cleavage of the core protein, yielding soluble PGs that retain the binding properties of the cell surface molecules. Shedding of the syndecan-1 and -4 ectodomains from the cell surface is accelerated by a variety of physiological regulators e.g. plasmin, activation of thrombin and EGF family members receptors, cellular stress (48; ML Fitzgerald, PW Park, M Bernfield, unpublished data) via activation of multiple intracellular signaling pathways, including unknown protein tyrosine kinase-dependent step(s). The proteolytic cleavage is within 15 amino acids of the plasma membrane and is mediated by a cell surface tissue inhibitor of metalloproteinase (TIMP)-3--sensitive metalloproteinase. Shedding is stimulated by tissue injury and these syndecan ectodomains are found in human inflammatory fluids where they modulate the activities of growth factors and proteinases (226, 245). See text for details.

Figure 9 Heparan sulfate proteoglycans alter proteinase activities depending on the antiprotease. The activities of some proteinases and antiproteases found in inflammatory fluids can be modified in vitro by heparin (246). This action can be duplicated by the soluble syndecan-1 ectodomain via its HS chains. For example, the soluble ectodomain binds neutrophil elastase tightly (Kd = 35 nM) apparently by the heparin-like domains of the HS chains (226) as shown here. This binding reduces the enzyme's affinity for its plasma-derived inhibitor, the serpin a 1-antiprotease. In skin wound fluids (left panel), elastase remains active because it is protected from this inhibition by soluble syndecan ectodomains. However, in inflammatory fluids of the respiratory tract (right panel), this binding increases the enzyme's affinity for the respiratory epithelium-derived secretory leukoprotease inhibitor (SLPI). Therefore, elastase activity is reduced owing to enhanced inhibition of the proteinase (V Kainulainen, ML Fitzgerald, M Bernfield, unpublished data). This effect of soluble HSPG ectodomains on protease and antiproteinases may
be a general mechanism for the modulation of extracellular proteolytic activity.

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Regulation of the cytoskeleton and cell adhesion by the Rho family GTPases in mammalian cells.

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ABSTRACT: Members of the Rho family of small Ras-like GTPases--including RhoA, -B, and -C, Rac1 and -2, and Cdc42--exhibit guanine nucleotide-binding activity and function as molecular switches, cycling between an inactive GDP-bound state and an active GTP-bound state. The Rho family GTPases participate in regulation of the actin cytoskeleton and cell adhesion through specific targets. Identification and characterization of these targets have begun to clarify how the Rho family GTPases act to regulate cytoskeletal structure and cell-cell and cell-substratum contacts in mammalian cells. The Rho family GTPases are also involved in regulation of smooth muscle contraction, cell morphology, cell motility, neurite

retraction, and cytokinesis. However, the molecular mechanisms by which the
Rho family GTPases participate in the regulation of such processes are not well established. Reprinted by permission of the publisher.

TEXT:

Key Words G protein, protein kinase, signal transduction, guanine nucleotide, cell morphology

INTRODUCTION

Dynamic rearrangements of the cytoskeleton and cell adhesion are required for various cellular processes, such as shape changes, migration, and cytokinesis (1-4). These temporal and spatial reorganizations of cell structure and cell contacts can be stimulated by extracellular signals, including growth factors, hormones, and other biologically active substances (1, 3, 4). The cytoskeleton consists mainly of three components: actin filaments, microtubules, and intermediate filaments (1, 3, 4). Cell-cell contacts are mediated by adhesion molecules, such as cadherins and their associated cytoplasmic proteins, a- and b-catenins (5-7). Cell-to-substratum contact is mediated by different types of adhesion molecules, such as integrins, and their interacting molecules, talin and vinculin (8, 9).

The Rho family GTPases (including Rho, Rac, and Cdc42) participate in regulation of the actin cytoskeleton and various cell adhesion events (10, 11). Rho has been implicated in the formation of stress fibers and focal adhesions (12), cell morphology (13), cell aggregation (14), cell motility (15), membrane ruffling (16), smooth muscle contraction (17, 18), neurite retraction in neuronal cells (19, 20), and cytokinesis (21, 22). Rac is involved in membrane ruffling (23), cell motility (24), actin polymerization (25), and cadherin-mediated cell-cell adhesion (26-28). Cdc42 participates in filopodia formation (29, 30) and cell-cell adhesions (28). The molecular mechanisms underlying the above processes have been largely unknown, until recently. Some of the molecular pathways that connect the Rho family GTPases to control of the cytoskeleton and cell adhesion have been established. The major emphasis in this review is on molecules that interact with the Rho family GTPases and their role in regulation of the cytoskeleton and cell adhesion.

MOLECULES THAT INTERACT WITH RHO FAMILY GTPASES

The Rho family GTPases belong to the Ras superfamily of small GTPases. At least 10 members of the Rho subfamily are known in mammals: RhoA-E, RhoG,
Rac1 and -2, Cdc42, and TC10. These proteins share >50[percent] sequence identity (31). RhoA, -B, and -C, Rac1 and -2, and Cdc42 are the best-studied members. RhoA, -B, and -C (collectively Rho) have the same amino acid sequence in their effector domains (approximately 32-41 amino acids), appear to be regulated in a similar manner, and seem to have similar functions. Like other GTP-binding proteins, the Rho family GTPases exhibit both GDP/GTP-binding and GTPase activities (31, 32). The GDP-bound
inactive and GTP-bound active forms are interconvertible by GDP/GTP exchange and GTPase reactions (31, 32). There are several groups of proteins that interact with the Rho family GTPases, including regulators and effectors.

GDP/GTP EXCHANGE PROTEINS

Guanine Nucleotide Exchange Factors There are guanine nucleotide exchange
factors (GEFs), also known as GDP dissociation stimulators (GDSs), that facilitate the release of GDP from the Rho family GTPases, thereby promoting the binding of GTP (33) because the cytosolic concentration of GTP is more than fivefold higher than that of GTP. GTP binding activates the Rho family GTPases. GEFs for the Rho family GTPases share a common sequence motif, designated the Dbl-homology (DH) domain (33). The Dbl proto-oncogene was originally isolated as cDNA that induced foci when transfected into NIH3T3 cells (33). In 1991, Dbl was shown to release GDP from Cdc42 in vitro (34). Since then, a number of GEFs for various Rho family GTPases (in parentheses) have been identified, including the following: Dbl (Cdc42, Rho); Lbc (Rho) (35); Lfc (Rho) (36); Lsc (Rho) (36); Tiam (Rac) (37); p115 Rho GEF (Rho) (38); Vav (Rac, Cdc42, Rho) (39); Fgd1 (Cdc42) (40); Trio (Rac, Rho) (41); Ost (Rho, Cdc42) (42); Bcr (Rac, Cdc42, Rho) (43); Pix (Rac) (44); and Smg GDS (Rac, Cdc42, Rho) (45). In addition to the DH domain, GEFs for the Rho family GTPases also contain a nearby pleckstrin homology (PH) domain (except for Smg GDS) (45). Both the
DH and PH domains are essential for GEF activity (33). As indicated, some Rho GEFs show activity toward several Rho family GTPases, whereas others have more restricted specificity. For example, p115 Rho GEF seems to be specific for Rho (38), whereas Fgd1 seems to be specific for Cdc42, at least in vitro (40). Vav is able to act on Rho, Rac, and Cdc42 in vitro (39, 46). Smg GDS was originally isolated as a GEF for Rap1, which is closely related to Ras (45, 47), but it was subsequently found to be active on both RhoA and K-Ras (48). Although a number of GEFs have been identified, the molecular mechanism by which their activity can be modulated by extracellular signals was unknown until recently (Figure 1).

Studies on heterotrimeric G proteins have clarified the mechanism by which p115 Rho GEF is regulated. Expression of constitutively active mutant forms of certain heterotrimeric G protein a subunits (Ga12 or Ga13) induce formation of stress fibers and focal adhesions in certain cells in a Rho-dependent manner (49). Mouse fibroblasts deficient in Ga13 fail to display thrombin-induced cell migration, which is also thought to require Rho (50). Examination of the sequence of p115 Rho GEF revealed that its NH2-terminal region has a regulator of G protein signaling domain (51). The regulator of G protein signaling domain of p115 Rho GEF specifically stimulates the intrinsic GTPase activity of Ga12 and Ga13 (51, 52). Conversely, activated Ga13 binds to p115 Rho GEF and stimulates its ability to catalyze nucleotide exchange on Rho (52). Thus, on stimulation by extracellular signals such as thrombin, activation of Ga13 is linked to activation of Rho via p115 Rho GEF (Figure 1).

Vav has DH, PH, and Src homology (SH2 and SH3) domains. Although Vav was originally thought to serve as a GEF for Ras (53), it actually functions as a GEF for Rac (39). Vav becomes phosphorylated on tyrosine residues when lymphoid cells are stimulated by antigens or mitogens. Tyrosine phosphorylation of Vav by a tyrosine kinase (Lck) enhances its GEF activity on Rac (39, 46). Rac is thought to be activated through processes that depend on phosphatidylinositol (PI) 3-kinase, because wortmannin (a relatively specific inhibitor of PI 3-kinase) or the expression of dominant-negative PI 3-kinase inhibits growth factor-induced Rac activation (54-58). Biochemical analysis showed that PI-3,4,5-triphosphate (a product of PI 3-kinase) enhances the phosphorylation and activation of Vav by Lck (59). Thus, activation of receptor-tyrosine kinases that recruit both Lck and PI 3-kinase may act synergistically to activate Vav, which in turn activates Rac. Further studies are required to identify the signaling molecules that couple other GEFs for the Rho family GTPases to upstream stimuli.

Rho GDP Dissociation Inhibitor GDP dissociation inhibitor (GDI) was originally isolated as a molecule that interacts specifically with GDPRho and inhibits the dissociation of GDP from Rho (32, 60, 61). In addition to Rho GDI itself, at least two other isoforms, named D4-GDI and Rho GDI3, have been identified (62, 63). Rho GDI was subsequently found to also be active on Cdc42 and Rac (64). Rho GDI prevents the binding of GDPRho, but not GTPRho, to cell membranes and can extract GDPRho from membranes (65).
Thus, in a sense, Rho GDI acts as a chaperone to regulate the translocation of the Rho family GTPases between membranes and the cytosol. In resting cells, the Rho family GTPases, including Rho, Rac, and Cdc42, exist mostly in the GDP-bound form and in complexes with Rho GDI in the cytosol (32). Because Rho GDI counteracts the action of GEFs, such as Dbl, it is thought that release of Rho GDI from Rho is necessary before Rho becomes susceptible to a GEF (66, 67). The molecular mechanism underlying dissociation of Rho GDI from Rho was unknown until recently. Biochemical analysis suggests a tentative model by which Rho GDI is released from Rho (68) (Figure 1). Rho GDI can be coimmunoprecipitated with moesin, a member of the ERM (ezrin, radixin, and moesin) family of proteins (69). In vitro, the NH2-terminal region of radixin binds to a GDPRho/Rho GDI complex, dissociates Rho GDI from GDPRho, and thereby enhances the ability of GEF to
induce GDP/GTP exchange (68). Thus, Rho GDI dissociation factors (GDFs), such as the ERM family proteins, which stimulate dissociation of Rho GDI from GDPRho, may play a critical role in regulating the GDP/GTP exchange reaction.

GTPASE-ACTIVATING PROTEINS

Rho GTPase-activating proteins (GAPs) were identified as molecules that stimulate the intrinsic GTPase activity of the Rho GTPases, leading to their conversion to the inactive GDP-bound state (32, 70). The first GAP identified for the Rho family GTPases was purified from cell extracts and designated p50 Rho-GAP (71). P50 Rho-GAP was subsequently found to be more

active on Cdc42 than on Rho or Rac (72). Since the discovery of p50 Rho-GAP, a number of GAPs for various Rho family GTPases (in parentheses) have been identified, including the following: Bcr (Rac > Cdc42) (73); Abr (Rac, Cdc42) (74); b-chimerin (Rac) (75); p190GAP (Rho > Rac, Cdc42) (76); 3BP-1 (Rac, Cdc42) (77); p122 Rho GAP (Rho) (78); Myr5 (Rho > Cdc42) (79); and RalBP1 (Cdc42 > Rac) (80). GAPs shares a related GAP homology domain that encompasses about 140 amino acids of the protein. The substrate specificity in vivo may be more restricted than in vitro, however.

Based on the preceding sections, the activity of the Rho family GTPases appears to be regulated cyclically, as follows (Figure 1). In the cytosol of the resting cells, the Rho family GTPases are present in the GDP-bound form complexed with Rho GDI. When cells are stimulated by certain
extracellular signals, Rho GDI is dissociated via the action of GDFs and specific GEFs for the Rho family GTPases are activated; then the GDP-bound
form of the Rho family GTPase is converted to the GTP-bound form. The GTP-bound form of Rho family GTPases is targeted to cell membranes by its COOH-terminal prenyl group and interacts with its specific targets (32, 65, 81). GAPs act as negative regulators by enhancing the GTPase activity of the Rho family GTPases and reconverting them to the inactive GDP-bound form. Rho GDI can then form a complex with the GDP-bound form and extract
it from the membrane back into the cytosol.

TARGETS/EFFECTORS

Rho Targets A number of proteins have been identified as targets of Rho by means of affinity chromatography, ligand overlay assay, or the yeast two-hybrid system. These targets include Rho-kinase/ROK/ROCK, the myosin-binding subunit (MBS) of myosin phosphatase, protein kinase N (PKN)/PRK1, rhophilin, rhotekin, citron, and p140 mDia (10) (Figure 2).

Rho-kinase was identified as a GTPRho-binding protein of extracts from bovine brain by affinity column chromatography on matrix-bound GTPRho (82).
Rho-kinase was also identified as ROKa (83) and ROCK2 (84). ROKb (85)/ROCK1
(86) is an isoform of Rho-kinase/ROKa/ROCK2. The kinase domain of Rho-kinase is situated at the NH2-terminal end and has 72[percent] sequence
homology with the catalytic domain of myotonic dystrophy kinase (82). Rho-kinase has a putative coiled-coil domain in its middle portion and a PH domain at its COOH-terminal end. GTP-bound Rho interacts with the COOH-terminal portion of the coiled-coil domain and activates the phosphotransferse activity of Rho-kinase (82). Rho-kinase is involved in regulation of smooth muscle contraction (87-89), the formation of stress fibers and focal adhesions (85, 90, 91), neurite retraction (92-94), and cytokinesis (95).

Myosin phosphatase is composed of three subunits: MBS, a 37-kDa type 1 phosphatase catalytic subunit, and a 20-kDa regulatory subunit (96). Myosin phosphatase binds to phosphorylated myosin light chain (MLC) via MBS and dephosphorylates it. The COOH-terminal domain of MBS interacts with GTP-bound Rho (88). Rho-kinase phosphorylates both MLC (87) and MBS, the
latter of which leads to inactivation of myosin phosphatase (88). Rho-kinase and MBS are therefore believed to regulate the level of MLC phosphorylation cooperatively, as described later.

PKN/PRK1 contains an NH2-terminal regulatory domain and a COOH-terminal catalytic domain. The catalytic domain is highly homologous to that of protein kinase C, whereas the NH2-terminal domain shares no obvious homology with protein kinase C or any other protein kinases (97). The regulatory domain contains three leucine zipper-like motifs. GTP-bound Rho interacts with the first leucine zipper-like motif in the NH2-terminal portion (98, 99) and activates the catalytic activity of PKN (98). The physiological functions of PKN/PRK1 are unknown. PRK2 is an isoform of PKN/PRK1 and appears to associate with GTPRac. PRK2 also interacts with Rho, but in a GDP/GTP-independent manner (100, 101). The expression of a kinase-deficient form of PRK2 disrupts actin stress fibers (101), which implicates PRK2 in actin cytoskeleton reorganization.

Rhophilin and rhotekin have sequence similarity to the Rho-binding domains of both MBS and PKN/PRK1 and interact with GTP-bound Rho (99, 102).
This region of homology represents one of the consensus motifs for a Rho-interacting surface. Rhophilin and rhotekin do not have any other diagnostic features in their primary structures, and their functions are unknown.

Citron was originally isolated as a Rho-binding protein in a yeast two-hybrid system (103). The overall domain structure of citron is similar in sequence to Rho-kinase, but it lacks a kinase domain. A splice variant of citron with an NH2-terminal kinase domain homologous to that of the Rho-kinase family (citron-kinase) was recently identified (104). Citron-kinase is localized at the cleavage furrow and mid-body during cytokinesis and this is implicated in cytokinesis (104).

p140mDia is a mammalian homologue of Drosophila melanogaster diaphanous, which is required for cytokinesis, and belongs to the formin-related family of proteins (105). p140mDia also has sequence similarity to yeast Bni1 (106). The NH2-terminal portion of p140mDia interacts with GTP-bound Rho. p140mDia also contains repetitive polyproline stretches that can bind profilin (105). p140mDia appears to be involved in actin polymerization (105).

Kv1.2, the delayed rectifier potassium channel, can associate with GTP-bound Rho (107). The overexpression of Rho reduces the basal current generated by exogenously expressed Kv1.2 in Xenopus oocytes. Clostridial C3 toxin, which ADP ribosylates and inactivates Rho (108, 148, 149), blocks the suppression of Kv1.2 current by one type (m1) of muscarinic acetylcholine receptors in human 293 embryonic kidney cell line. Thus, G protein-coupled receptors may activate Rho, which in turn regulates Kv1.2 activity.

Phospholipase D (PLD) is thought to be activated by Rho (109), although the molecular mechanism is not known. PLD hydrolyzes phospholipids
to yield phosphatidic acid and their head groups. Phosphatidic acid is claimed to be a direct second messenger (109, 110), but it can also be metabolized to other demonstrated second messengers, including diacylglycerol and lysophosphatidic acid (LPA). The activity of PLD is stimulated by a variety of extracellular signals, such as growth factors and hormones. Biological and biochemical studies have indicated that Rho regulates PLD activity cooperatively with Arf, another member of the Ras-related superfamily of small GTPases (111-114).

PI 5-kinase has been implicated in Rho signaling (115, 116). Previous work has shown that PI 4,5-bisphosphate (PIP2), the product of PI 5-kinase, can regulate the interactions of a number of actin-binding proteins, including profilin, a-actinin, gelsolin, and p39CapZ in vitro (117). Thus, it is possible that alterations in PIP2 synthesis affect actin polymerization and the association of actin filaments with focal adhesion zones. However, whether effects on PIP2 are part of a mechanism by which Rho controls the cytoskeleton in intact cells remains controversial.

Rac/Cdc42 Targets A number of proteins have been identified as targets for Rac and/or Cdc42, including p21-activated kinases (PAKs), WASP/N-WASP,
IQGAP1, MRCK, Por1, p140Sra-1, and Posh. It is interesting that several of these proteins interact with both Rac and Cdc42 (10) (Figure 3).

To date, at least three isoforms of PAK (PAK1-3) have been identified (118-122). PAKs are serine/threonine kinases, which comprise an NH2-terminal regulatory domain and a COOH-terminal catalytic domain (118).
In the NH2-terminal region, there is a conserved domain of approximately 20
residues that is responsible for interaction with Cdc42/Pac; this motif is called the CRIB (Cdc42/Rac-interactive binding) site (123). Several other potential targets for Cdc42 and Rac share this motif (see below). The GTP-bound forms of Cdc42 and Rac1 interact with the CRIB site and activate
all PAK isoforms (118-122). PAKs are components of pathways that regulate cell morphology, including formation of lamellipodia and disassembly of stress fibers and focal adhesions (124, 125). PAKs are also upstream elements in the JNK and p38 kinase pathways that control gene expression (126, 127). PAK interacts with Pix, a GEF for Rac (44). This interaction is necessary for PAK-induced lamellipodia formation (128). Moreover, the PAK-induced lamellipodia formation is inhibited by dominantnegative Rac (RacN17). Hence, Cdc42-dependent activation of PAK leads to Pixmediated activation of Rac.

The WASP gene was originally identified as the locus mutated in patients with Wiskott-Aldrich syndrome (129). Its neural isoform, N-WASP, was identified as a molecule interacting with the SH3 domain of Grb2/Ash (130). The WASP and N-WASP molecules consist of PH, CRIB, proline-rich, verprolin-homologous, and cofilin-like domains (129, 130). N-WASP, but not WASP, also contains an IQ motif, which is able to bind calmodulin. WASP is expressed exclusively in hematopoietic cells, whereas N-WASP is ubiquitously expressed, although especially abundant in brain (131). WASP and N-WASP interact with GTP-bound Cdc42 and induce actin

polymerization
when overexpressed (129, 131). NWASP appears to play a crucial role in filopodia formation (131).

The IQGAP1 gene was originally isolated as a member of the RAs GAP family (132, 133). However, no GAP activity toward any small GTPases has been demonstrated for IQGAP1. At least two isoforms of IQGAP have been identified, IQGAP1 and IQGAP2. Both isoforms directly interact with GTP-bound Cdc42 and Rac, but not with the GDP-bound forms (134-137). IQGAP1
consists of a calponin-homologous domain, IQGAP-repeat sequences that are the hallmarks of IQGAP1 and IQGAP2, a WW domain, an IQ motif, and a GRD
sequence (Ras-GAP related domain). IQGAPs, unlike PAKs and WASP, do not contain a CRIB site; the COOH-terminal GRD domain is responsible for the interaction with Cdc42. IQGAP1 (138, 139) and IQGAP2 (140) directly interact with actin filaments and cross-link the actin filaments, and GTP-bound Cdc42 enhances the cross-linking activity (138). In addition to its role in actin filament organization, IQGAP1, acting downstream of Cdc42 and Rac1, appears to regulate cell-cell adhesion through the cadherin-catenins pathway, as described below (141).

MRCKa and -b interact with GTP-bound Cdc42 through a CRIB site (142). MRCKs are composed of an NH2-terminal kinase domain, a coiled-coil region, a cysteine-rich segment, a PH motif, and a CRIB site. The kinase domains of MRCKs show sequence similarity with those of myotonic dystrophy kinase and
Rho-kinase. MRCKa is colocalized with Cdc42 at the cell periphery (142). MRCKs appear to regulate the formation of focal adhesive complexes and filopodia in a Cdc42-dependent manner. Gek, a D. melanogaster ortholog of MRCK, binds to Cdc42 in a GTP-dependent manner (143). Homozygous gek mutants die as larvae, and egg chambers homozygous for gek mutations exhibit an abnormal accumulation of F-actin and are defective in producing fertilized eggs (143).

Por1, p140Sra-1, and Posh have been identified as Rac-specific targets (144-146). Por1 and p140Sra-1 may participate in regulation of lamellipodia formation (144, 145), whereas Posh may regulate JNK activity (146).

%%%BACTERIAL%%% TOXINS

The Rho family GTPases are targets for at least three groups of %%%bacterial%%% toxins that either inactivate or activate the GTPases (147). The first group is the C3 exoenzyme family. Members of this toxin family include Clostridium botulinum C3 ADP-ribosyltransferase, Clostridium limosum transferase, Bacillus cereus transferase, and epidermal differentiation inhibitor (EDIN). C. botulinum C3 toxin is a useful tool for identifying specific functions of Rho. C. botulinum C3 toxin specifically ADP ribosylates Rho at Asn41 using NAD as the donor substrate (148, 149). ADP ribosylation of Rho is thought to interfere with the ability of Rho to interact with its putative targets, thereby inhibiting the functions of Rho. C. botulinum C3 toxin ADP ribosylates only poorly other Rho family members, such as Rac and Cdc42.

%%%Bacterial%%% toxins in the second group are large clostridial cytotoxins. Members of this toxin family include Clostridium difficile toxins A and B and Clostridium sordellii HT and LT (147). C. difficile toxins specifically glycosylate Rho at Thr37, Rac at Thr35, and Cdc42 at Thr35 by using UDP-glucose as the donor substrate (150). The biological effects of C. difficile toxins indicate that glycosylation inactivates the Rho family GTPases (151).

The third group is cytotoxic necrotizing factors (CNFs). Members of this toxin family include Escherichia coli CNF1 and CNF2 and Bordetella spp. DNTs (147). CNFs induce a deamidation of Gln63 of Rho, resulting in its conversion to Glu63 (152). Loss of Gln63 inhibits both the intrinsic and the GAP-stimulated GTPase activity of Rho, thereby sustaining Rho in its active GTP-bound form (152). CNF acts on Cdc42 as well as on Rho. Thus, CNFs may activate several Rho family GTPases in vivo.

FUNCTIONS OF THE RHO FAMILY GTPASES

SMOOTH MUSCLE CONTRACTION AND CONTRACTILITY

Specific agonists, such as carbacol and endothelin, cause an increase in cytosolic Ca2+ and subsequent activation of Ca2+/calmodulin-dependent MLC kinase in smooth muscle. MLC kinase phosphorylates MLC and activates myosin
ATPase, thereby inducing contraction of smooth muscles (153-155). However,
because the levels of MLC phosphorylation and degree of contraction are not always proportional to the cytosolic Ca2+ levels, an additional mechanism that regulates MLC phosphorylation and contraction has been proposed
(156).
Because the agonist-induced MLC phosphorylation and contraction of permeabilized smooth muscles occur at fixed suboptimal concentrations of Ca2+ and are GTP dependent, a GTP-binding protein is thought to be involved in receptor-mediated sensitization of MLC phosphorylation (157, 158).

Evidence that Rho is the GTP-dependent factor involved in sensitizing smooth muscle contraction at suboptimal Ca2+ levels has been obtained in several laboratories (159). GTP-bound Rho causes contraction of permeabilized smooth muscles at fixed suboptimal concentrations of Ca2+ (17), and C. botulinum C3 toxin and EDIN inhibit contraction induced by the guanosine 5'-(3-O-thio)-triphosphate (GTPgS) (a nonhydrolyzable GTP analog)
(17). C. botulinum C3 toxin inhibits the GTPgS-induced MLC phosphorylation in permeabilized smooth muscle cells (160). GTP-bound Rho stimulates MLC phosphorylation in permeabilized smooth muscle, and EDIN inhibits the ability of carbacol-induced Ca2+ elevation to stimulate MLC phosphorylation (18).

Until recently, the molecular mechanism by which Rho regulates MLC phosphorylation was largely unknown. Recent analyses suggest the model shown in Figure 4, in which Rho regulates MLC phosphorylation through its effectors, Rho-kinase and MBS (87, 88). GTP-bound Rho interacts with both Rho-kinase and MBS of myosin phosphatase, resulting in activation of Rho-kinase and translocation of MBS. Activated Rho-kinase phosphorylates MBS, thereby inactivating myosin phosphatase (88). Concomitantly, Rho-kinase phosphorylates MLC at the same site that is phosphorylated by MLC kinase and activates myosin ATPase (87). Both events appear to be necessary for an increase in MLC phosphorylation. Consistent with this view, addition of dominant-active Rho-kinase to permeabilized vascular smooth muscle induces contraction through MLC phosphorylation (89). A specific chemical inhibitor for Rho-kinase (Y27632) has recently been developed (161). Y27632 selectively inhibits smooth muscle contraction by inhibiting GTP-dependent sensitization to suboptimal Ca2+ and suppresses hypertension in several hypertensive rat models (161) as well as vasospasm of porcine coronary artery (H Shimokawa, unpublished observations). Thus, Rho-kinase-mediated sensitization of smooth muscle contraction may be involved in the pathophysiology of hypertension and vasospasm.

In nonmuscle cells, MLC phosphorylation is thought to modulate interaction of myosin with actin to regulate stress fiber contraction and thereby affect cell motility (162). Several studies have established roles for Rho and Rho-kinase in MLC phosphorylation in nonmuscle cells. MBS is phosphorylated, and myosin phosphatase activity is inactivated, during the action of thromboxane A2 in platelets, and both responses are blocked by prior treatment of platelets with C. botulinum C3 toxin (163). Similar observations have been made in endothelial cells responding to thrombin (164). Expression of dominant-active Rho (RhoV14) or constitutively active Rho-kinase induces MLC phosphorylation in COS7 cells (165) and NIH3T3 cells
(92), whereas the expression of a dominant-negative Rho-kinase variant inhibits serum-induced MLC phosphorylation (92). Thus, Rho-kinase appears to regulate MLC phosphorylation downstream of Rho in nonmuscle cells as well as in smooth muscle.

STRESS FIBERS AND FOCAL ADHESIONS

Rho is believed to regulate the formation of actin stress fibers and focal adhesions, based on the following observations. Confluent, serum-starved Swiss 3T3 cells have few actin stress fibers, which are composed of actin filaments and associated myosin filaments that confer contractility to the fibers on MLC phosphorylation (162). When these cells are stimulated by LPA, new stress fibers, which increase in number and diameter, appear (12). Prior treatment of the cells with C. botulinum C3 toxin inhibits LPA-induced stress fiber formation. Microin-jection of RhoAV14 into the cells induces stress fiber formation (12, 13). Rho is also required for the LPA-induced formation of focal adhesions (12), the sites at which stress fibers are linked via integrins to extracellular matrix components, such as fibronectin (8, 9). Certain molecules, including vinculin, a-actinin, and talin, assemble with integrin that form the focal adhesions and serve as the anchors for stress fibers. Expression of dominant-active Rho-kinase induces formation of stress fibers in Swiss 3T3 and MDCK cells, whereas the
expression of dominant-negative Rho-kinase inhibits the LPA- or RhoAV14-induced formation of stress fibers (85, 90, 91). The expression of MLC mutant, MLCT18D,S19D (substitution of Thr and Ser by Asp), which is known to cause activation of myosin ATPase and a conformational change of myosin II when reconstituted with myosin heavy chain in vitro (166-168), also enhances the formation of stress fibers and focal adhesions (92).

Pharmacological analysis suggests that contractility of stress fibers driven by MLC phosphorylation governs focal adhesion formation (169). Taken together, these observations indicate that Rho through Rho-kinase plays a critical role in the formation of stress fibers and focal adhesions via myosin II activation (Figure 5).

LAMELLIPODIA AND FILOPODIA

Membrane ruffling, which is characterized by dynamically fluctuating movement of membrane protrusions consisting of lamellipodia and filopodia, is rapidly induced in cells in response to certain extracellular signals (170). The molecular mechanism of membrane ruffling is not known, but it has been suggested that polymerization and depolymerization of actin beneath the plasma membrane drives the process (171). Accumulating evidence indicates that Rac serves as a key control element in lamellipodia formation and membrane ruffling induced by certain growth factors, such as platelet-derived growth factor, and by activated Ras in fibroblasts (23), whereas Cdc42 appears to regulate filopodia formation (29, 30). Injection of dominant-active Rac (RacV12) triggers lamellipodia and membrane ruffling followed by stress fiber formation, whereas injection of dominant-negative RacN17 inhibits these processes induced by the same growth factors (23). Injection of dominant-active Cdc42 (Cdc42V12) rapidly induces filopodia formation followed by lamellipodia and membrane ruffling (29, 30). The cytoskeletal changes induced by Rac and Cdc42 are associated with integrin-based focal complexes distinct from the adhesion sites induced by Rho (23, 29, 30). Judging from the kinetics of the cytoskeletal changes induced by Rho, Rac, and Cdc42, cross talk appears to exist: Cdc42 can activate Rac, and Rac can activate Rho (11). It should be noted that Rho is implicated in the membrane ruffling (lamellipodia) induced by hepatocyte growth factor (HGF) and 12-O-tetradecanoylphorbol-13-acetate in certain cells, such as KB cells (16) and MDCK cells (172), whereas Rac is implicated in the insulin-induced membrane ruffling in KB cells (16). These observations indicate that Rho and Rac receive distinct signals but generate similar outputs in certain cells. This convergence could be partly explained by the fact that Rho and Rac/Cdc42 interact with different protein kinase targets; nevertheless, these enzymes share a high degree of similarity in their catalytic domains, for example Rho-kinase and MRCKa.

The molecular mechanisms by which Rac and Cdc42 regulate lamellipodia and filopodia, respectively, are still largely unknown. Several targets of Rac and Cdc42 have been implicated in these processes.

Accumulating evidence suggests that cofilin plays a critical role in the rapid turnover of actin filaments in various cellular processes, including lamellipodia formation (171). Cofilin sequesters actin monomers and severs actin filaments, thereby inducing disassembly of actin filaments in vitro (171). Phosphorylation of cofilin at Ser3 reduces its actin-binding and -severing activities (173, 174). Recent studies indicate a role for LIM-kinase in Rac-induced lamellipodia formation, which appears to be mediated by the phosphorylation of cofilin (175, 176). Dominant active Rac (RacV12) activates LIM-kinase (175, 176), although the linkage between Rac and LIM-kinase is unknown. The expression of dominant-negative LIM-kinase inhibits RacV12-induced membrane ruffling. Activated LIM-kinase phosphorylates cofilin at Ser3, which may prevent cofilin from disassembling of actin filaments and inhibits the ability of cofilin to bind actin monomers, thereby promoting the formation of the proper actin meshwork for lamellipodia. Rac may also increase the production of PIP2 through the action of PI 5-kinase (177). The change in PIP2 levels may affect the functions of certain classes of actin-binding proteins and influence actin polymerization by uncapping or increased nucleation of actin filaments, perhaps in cooperation with cofilin (178).

Por1, a specific target of Rac, may participate in lamellipodia formation (144). A mutation in the effector-binding loop of Rac1 abolishes membrane ruffling and also the interaction of Rac with Por1. Truncated versions of Por1 inhibit the induction of membrane ruffling by RacV12 in fibroblasts. In addition, the overexpression of Por1 synergizes with dominant-active Ras (RasV12) in the induction of membrane ruffling, which suggests a potential role of Por1 in Rac1-mediated membrane ruffling. p140Sra-1, another Rac-specific target, is colocalized with activated Rac in the membrane ruffling area (145). p140Sra-1 directly interacts with actin filaments. IQGAP1, a target of Rac and Cdc42, specifically accumulates at the membrane ruffling area induced by insulin or RacV12 (135). IQGAP1 (138) and IQGAP2 (139) directly interact with and cross-link actin filaments. A calponin-homologous domain mediates the interaction of IQGAP1 and IQGAP2 with actin filaments (138). GTP-bound Cdc42, but not its GDP-bound form, enhances the actin filament cross-linking activity of IQGAP1 in vitro (138). These proteins, including LIM-kinase, Por1, p140Sra-1, and IQGAPs, may contribute to formation of the actin meshwork required for membrane ruffling, although their relation is largely unknown.

The expression of N-WASP, but not WASP, enhances Cdc42-induced filopodia formation (130). Injection of anti-N-WASP antibody specifically blocks bradykinin-induced filopodia formation (131). Moreover, N-WASP severs actin filaments in vitro, and this activity is further enhanced by GTP-bound Cdc42, but not the GDP-bound form (131). Thus, N-WASP appears to play a crucial role in filopodia formation.

MRCKa is colocalized with Cdc42 at the cell periphery in HeLa cells (142). MRCKa preferentially phosphorylates MLC at Ser19 in vitro, as observed for Rho-kinase (142). The expression of Cdc42V12 or constitutively active MRCKb induces MLC phosphorylation in COS7 cells (T Nakamura, unpublished data). The expression of dominant-negative MRCKa blocks the Cdc42V12-dependent formation of filopodia and focal complexes. The coexpression of MRCKa enhances the Cdc42V12-induced formation of filopodia, which suggests that MRCKa regulates filopodia formation, presumably through reorganization of actin-myosin complexes.

CELL MOTILITY AND MIGRATION

Reorganization of actin filaments and cell-substratum contacts is believed to be involved in cell motility. Membrane ruffling is observed at the leading edge of motile cells and is also thought to be essential for cell motility (179). A force arising from actin polymerization appears to drive lamellipodial protrusion (4), which is thought to be regulated by Rac (11, 23) (Figure 6). Actin at the area of membrane ruffling is thought to be continuously depolymerizing and repolymerizing during cell movement (4). A force derived from myosin II triggered by MLC phosphorylation, which appears to be regulated by Rho (87, 88), in the area of membrane ruffling and in the posterior region of motile cells may also contribute to cell movement (4, 180) (Figure 6). Indeed, injection of anti-MLC kinase diminishes the cell motility of macrophages (181) (Figure 6).

Accumulating evidence indicates that the Rho family GTPases regulate cell motility (15, 24, 182). %%%Scatter%%% %%%factor%%%/HGF stimulates the motility of epithelial cells, initially inducing a centrifugal spreading of cell colonies followed by a disruption of cell-cell adhesions and then cell scattering, accompanied by membrane ruffling. Roles of the Rho family GTPases in cell motility have been investigated mainly by two groups of investigators. Takaishi et al (15) have reported that HGF-induced cell motility of keratinocytes (308R cells) is inhibited by microinjection of either Rho GDI or C. botulinum C3 toxin, but not by microinjection of RacN17. The action Rho GDI is counteracted by comicroinjection of activated Rho, but not of activated Rac, indicating that Rho is necessary for the HGF-induced cell motility. Conversely, Ridley et al (24) have proposed that Rac, rather than Rho, is necessary for the HGF-induced cell motility of MDCK cells and that activated Rho inhibits the HGF-induced motility. These apparent contradictory results concerning the roles of Rho and Rac might be explained by the differences in cell types and reagents used. A more recent study has shown that the expression of RhoN19 or RacN17 inhibits the HGF-induced membrane ruffling of MDCK cells (172). Thus, both Rho and Rac may play crucial roles in the motility of MDCK cells. The expression of dominant-negative Rho-kinase also inhibits the HGF-induced membrane ruffling and wound-induced cell migration, indicating that Rho-kinase is involved in cell motility (172).

Taken together, the above observations suggest that MLC phosphorylation regulated by Rho and Rho-kinase is necessary for cell motility. In addition to using MLC as a substrate, Rho-kinase also phosphorylates adducin and moesin directly and inactivates myosin phosphatase which dephosphorylates adduction and moesin, thereby increasing phosphorylation levels of adducin and moesin (172, 183-185). Adducin binds to F-actin and to the spectrin-F-actin complex (186, 187). Adducin subsequently promotes the binding of spectrin to F-actin or the spectrin-F-actin complex to form a spectrin-F-actin meshwork (186, 187). Adducin accumulates within the spectrin-F-actin meshwork at cell-cell contact sites and membrane ruffling areas (188). The phosphorylation of

a-adducin by Rho-kinase enhances the interaction of a-adducin with F-actin (185). Rho-kinase phosphorylates a-adducin at Thr445 in the membrane ruffling area of MDCK cells during the action of HGF (172). The expression of a-adducinT445A,T480A (substitution of Thr residues by Ala), which is not phosphorylated by Rho-kinase, inhibits HGF-induced membrane ruffling and wound-induced cell migration. The expression of a-adducinT445D,T480D (substitution of Thr residues by Asp), which may mimic a-adducin phosphorylated by Rho-kinase, counteracts the inhibitory effect of dominant-negative Rho-kinase on HGF-induced membrane ruffling and wound-induced cell migration. Thus, phosphorylation of adducin by Rho-kinase appears to be necessary for membrane ruffling and cell motility.

NEURITE RETRACTION AND EXTENSION

Chemoattractants and chemorepellants can exert significant effects on neural architecture, ranging from the stimulation of neurite outgrowth to the induction of growth cone collapse and neurite retraction (189, 190). The growth cone is a dynamic structure at a tip of a neurite and consists of filopodia and lamellipodia. Neurite extension is thought to be driven by actin polymerization in growth cones. Neurite retraction and the extension of developing neurites evoked by extracellular molecules are fundamental to nervous system development and neural plasticity. Rho is implicated in thrombin-, serum-, and LPA-induced neurite retraction and cell rounding in N1E-115 neuroblastoma and PC12 cells (19, 191), whereas Rac and/or Cdc42 is implicated in the promotion of filopodia and lamellipodia formation in growth cones and therefore in neurite extension (192). Competition appears to exist between chemoattractant- and chemorepellant-induced morphological pathways mediated by Rac and/or Cdc42 and by Rho, leading to either neurite development or collapse (192). The Rho-induced neurite retraction is presumed to be driven by a contraction of the cortical actin-myosin system (20), which is known to be regulated by Rho. Consistent with this conclusion, the expression of dominant-active Rho-kinase induces neurite retraction (92-94), whereas the expression of dominant-negative Rho-kinase inhibits the LPA-induced neurite retraction. The expression of mutant MLCT18D,S19D also enhances neurite retraction (92). Thus, myosin II activation appears to promote neurite retraction downstream of Rho and Rho-kinase.

CELL-CELL ADHESION

Cell-cell adhesions are categorized into several types, including tight junctions and adherens junctions (5-7, 193). Tight junctions, the most apical component of the junctional complex in columnar epithelium, form a diffusion barrier that regulates the flux of ions and hydrophilic molecules. Among the proteins that comprise tight junctions are claudin and occludin. Rho is thought to be required to maintain the "fence" function of the tight junction in epithelial cells (194, 195).

Adherens junctions are characterized by a well-developed plaque structure in which actin filaments are densely associated. Adherens junctions are composed of adhesion molecules such as cadherin (5). a- and b-Catenins are cadherin-associated cytoplasmic proteins that are required for cadherin-mediated cell-cell adhesion (5, 194). b-Catenin serves as a bridge between cadherin and a-catenin (Figure 7). a-Catenin is thought to link cadherin and catenins with actin filaments. Recent work has suggested that Rho, Rac, and Cdc42 are required for maintaining cadherin-mediated cell-cell adhesion (26-28). The expression of either Cdc42N17 or RacN17 in L cells expressing E-cadherin (EL cells), but not in L cells expressing E-cadherin-a-catenin chimeric protein (nEaCL cells), results in a reduction of E-cadherin-mediated cell-cell adhesive activity (M Fukata, unpublished observation). Because b-catenin is not required for the adhesion of nEaCL cell, Cdc42 and Rac appear to regulate E-cadherin-mediated cell-cell adhesion presumably through b-catenin.

Until recently, the mechanism underlying the regulation of E-cadherin-mediated cell-cell adhesion by the Rho family GTPases had been unknown. Studies of IQGAP, a target of Cdc42/Rac, have shed light on the molecular mechanism as follows (141). IQGAP1 is localized with E-cadherin and b-catenin at cell-cell contact sites in MDCK cells and EL cells, but not in nEaCL cells, indicating that IQGAP1 accumulates at cell-cell contact sites in a manner dependent on E-cadherin, b-catenin, or the NH2-terminal domain of a-catenin (141). IQGAP1 interacts with E-cadherin and b-catenin both in vivo and in vitro (141). IQGAP1 promotes the dissociation of a-catenin from a cadherin-catenin complex in vitro and in vivo (141). These IQGAP1 effects are reversed by activated Cdc42. The overexpression of IQGAP1 in EL cells, but not in nEaCL, results in reduction of E-cadherin-mediated cell-cell adhesive activity. The inhibitory effect of IQGAP1 is counteracted by the coexpression of Cdc42V12 (141). Thus, activated Cdc42 blocks the ability of IQGAP1 to inhibit assembly of a cadherin-catenins complex and thereby promotes formation of adherens junctions (Figure 7).

MICROVILLI

The ERM family proteins are essential components of microvilli-like structures (apical membrane protrusions) on polarized epithelial cells, fibroblasts, and lymphocytes (196-200) and are localized at the specific regions where actin filaments associate with plasma membranes, such as at the brush border of the intestinal epithelial cells, in cleavage furrows, at membrane ruffles, in filopodia, at cell-cell adhesion sites, and at other microvilli-like structures (193, 198, 201-206). The ERM family proteins function as bridges between the plasma membrane and actin filaments (198-200). The NH2-terminal domains of the ERM family proteins are thought to bind directly to some integral membrane proteins, such as CD44 (207), and the COOH-terminal domains of ERM proteins bind to actin filaments (208, 209). The NH2- and COOH-terminal domains appear to mask each other, presumably through the intramolecular head-to-tail association between the NH2- and COOH-terminal domains, thereby preventing the interaction of the ERM family proteins with their partners (210, 211). Once this intramolecular occlusion is relieved, the ERM family proteins are activated and translocate from the cytosol to the plasma membranes, where they serve to anchor actin filaments (212, 213). Formation of the complex between CD44 and the ERM family members appears to be regulated dynamically. Recent evidence suggests that Rho regulates formation of the complex between CD44 and the ERM family proteins (69). A permeable cell reconstitution assay showed that the ERM family proteins are essential for Rho- and Rac-induced cytoskeltal reorganization (214).

How does Rho regulate the activity of the ERM family proteins? In thrombin-activated platelets, moesin is phosphorylated at Thr558 (215). This phosphorylation is observed at filopodia in macrophages and is thought to be required for the stable interaction of moesin with actin (216). Recent biochemical analysis has shown that Rho-kinase phosphorylates moesin at Thr558, thereby inhibiting intramolecular association between the NH2- and COOH-terminal domains of moesin (183, 185). Presumably Rho acts in vivo through Rho-kinase to phosphorylate and activate the ERM family proteins. Other studies have shown that LPA stimulation of serum-starved NIH3T3 cells results in relocalization of radixin into microvilli-like structures, which is blocked by C. botulinum C3 toxin (217). The expression of RhoV14 induces formation of microvilli-like structures and localizes radixin or moesin into these structures in both Rat1 and NIH3T3 cells. A more recent analysis has shown that the expression of RhoV14 in COS7 cells induces moesin phosphorylation and formation of microvilli-like structures at apical membranes where Thr558-phosphorylated moesin accumulates, whereas the expression of dominant-negative Rho-kinase inhibits both these processes (218). The expression of dominant-active Rho-kinase also induces moesin phosphorylation and formation of microvilli-like structure. The expression of moesinT558D (substitution of Thr by Asp), which may mimic phosphorylated moesin, induces formation of microvilli-like structures, whereas the expression of moesinT558A (substitution of Thr by Ala), which is not phosphorylated by Rho-kinase, inhibits the RhoV14-induced formation of microvilli-like structures (218). Thus, Rho-kinase does appear to regulate moesin phosphorylation downstream of Rho in vivo, and the phosphorylation of moesin by Rho-kinase seems to play a crucial role in the formation of microvilli-like structures.

CYTOKINESIS

Cells undergo cytokinesis at the end of M-phase of the cell cycle through the formation of a contractile ring beneath the plasma membrane. The contractile ring is composed mainly of actin filaments and myosin and contraction of this structure is thought to provide the force required to divide the cells into two daughter cells by pulling the membrane inward (cytoplasmic division) (2, 219). The cytoplasmic division of fertilized Xenopus laevis embryos is inhibited by microinjection of Rho GDI or C. botulinum C3 toxin, whereas nuclear division occurs normally (21, 22, 220). Coinjection of Rho GDI with activated RhoA prevents Rho GDI action. Thus, Rho appears to control cytoplasmic division through regulation of the

contractility of the contractile ring.

Rho and Rho-kinase accumulate at the cleavage furrow (221, 222), where MLC phosphorylation occurs (180). The expression of dominant-negative Rho-kinase inhibits cytokinesis in Xenopus embryo and in mammalian cells, resulting in multinucleate cells (95). Thus, MLC phosphorylation by Rho-kinase may promote contraction of the contractile ring and play a critical role in cytokinesis. Rho-kinase also phosphorylates intermediate filament proteins, such as glial fibrillary acidic protein (GFAP) and vimentin (223, 224), MBS, and the ERM family proteins (Y Kawano, unpublished observations), exclusively at the cleavage furrow during cytokinesis. The expression of GFAP mutated at its Rho-kinase phosphorylation sites results in impaired glial filament segregation into postmitotic daughter cells (95). These results suggest that Rho-kinase is essential not only for cytokinesis but also for segregation of GFAP filaments into daughter cells, which in turn ensures efficient cellular separation.

Citron-kinase is localized at the cleavage furrow and midbody (104). The overexpression of kinase-deficient or constitutively active mutant of citron-kinase results in multinucleate cells, whereas that of a constitutively active kinase causes abnormal contraction during cytokinesis, which suggests that citron-kinase is involved in cytokinesis. The physiological substrates of citron-kinase remain to be identified.

CELL TRANSFORMATION

Transformed cells show altered patterns of expression of cytoskeletal proteins and commonly have a disorganized actin cytoskeleton, which may be associated with the ability of transformed cells to grow in an anchorage-independent fashion (225). Ras-transformed fibroblasts typically show decreased numbers of actin stress fibers and possess sparse, less-prominent focal adhesions, which are localized only at the margins of cells, whereas Vav- and Dbl-transformed cells show well-developed stress fibers and focal adhesions (226). The critical involvement of the Rho family GTPases including Rho, Rac, and Cdc42, in Ras-induced transformation is supported by a number of experiments (227-230; see also 58, 231-233). Rac appears to participate in the Ras-induced low serum growth, whereas Cdc42 appears to participate in the Ras-induced anchorage independence (229). Although Rho activity is required for the Ras-induced foci formation, Rho activity may be down-regulated in stably transformed Rat1 cells because stress fibers and focal adhesions decrease in number at that stage (228). Consistently, Rat1 cells expressing RasV12 show a severe disruption of actin stress fibers and cell adhesions, whereas the coexpression of RhoV14 restores not only the formation of stress fibers and focal adhesions, but also cell-cell adhesions (234). The coexpression of constitutively active Rho-kinase restores the assembly of stress fibers and focal adhesions (234). The treatment of Rat1 cells with LPA enhances stress fiber formation, whereas it fails to induce stress fiber formation in cells expressing RasV12 (234). Thus, Rho-kinase may be inactivated in cells expressing RasV12, and this may contribute to oncogenic Ras-induced transformation. Because the expression of Cdc42V12 or constitutively active PAK decreases the number of stress fibers and focal adhesions (124), Cdc42,
acting through PAK, may inactivate the Rho and/or Rho-kinase. However, Ras-transformed MCF10A breast epithelial cells display a fibroblastic morphology with decreased cell-cell adhesions but increased focal adhesions and stress fibers (233, 235). Thus, the terminal morphologies of Ras-transformed cells may depend on cell types.

OTHER FUNCTIONS OF THE RHO FAMILY GTPASES

The Rho family GTPases have been reported to regulate various cell functions, including transcription, cell growth, endo-exocytosis of vesicles, and development in mammals (10) and lower eukaryotes (236). Because this review focuses on the regulation of cytoskeletons and cell adhesions in mammals, the above functions regulated by the Rho family GTPases are not described in detail for such information, the reader is referred to two excellent reviews (10, 11) .

PERSPECTIVES

To understand the mechanism by which the Rho family GTPases regulate the cytoskeletons and cell adhesion, enormous effort has been made over the past several years to identify upstream regulators and downstream effectors
of the Rho family GTPases. As a result, a number of the regulatory proteins and targets have been isolated. Intensive analyses of their functions have provided some insights into the modes of activation and action of the Rho family GTPases at the molecular level. For example, Rho-kinase has critical roles in divergent pathways downstream of Rho. Rho-kinase is involved in MLC phosphorylation, leading to the formation of stress fibers, focal adhesions, and neurite retraction, indicating a direct linkage between the Rho family GTPases and the cytoskeleton. Further studies will lead to a better understanding of how temporal and spatial signals are delivered to the cytoskeletons and cell contact sites through the Rho family GTPases and their targets.

Added material

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Figure 1 Mode of activation of the Rho family GTPases. GEF, Guanine nucleotide exchange factors; GAP, GTPase-activating proteins; GDI, GDP dissociation inhibitor; GDF, GDI dissociation factor.

Figure 2 Mammalian targets of Rho. PIP, Phosphatidylinositol 4,5-bisphosphate; PKN, protein kinase N.

Figure 3 Mammalian targets of Rac and Cdc42. PIP, Phosphatidylinositol 4,5-bisphosphate; PI, phosphatidylinositol; PAK, p21-activated kinases.

Figure 4 Model for regulation of MLC (myosin light chain) phosphorylation by Rho, Rho-kinase, and myosin phosphatase. cat, Catalytic subunit; MBS, myosinbinding subunit.

Figure 5 Model for formation of focal adhesions induced by the Rho/Rho-kinase pathway.

Figure 6 Roles of Rho and Rac in cell motility. MLC, Myosin light chain.

Figure 7 Role of IGQAP1 in regulation of E-cadherin-mediated cell-cell adhesion. E, E-cadherin; a, a-catenin; b, b-catenin.

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Regulation of the movement of solutes across tight junctions.
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ABSTRACT: The intercellular tight junction is the rate-limiting barrier in the paracellular pathway for permeation by ions and larger solutes. A variety of widely used electrical and flux approaches are used in the analyses of solute permeation through this pathway; however, each has limitations in practice. It is now clear that solute permeation across tight junctions is dynamically regulated by intracellular events with a common effector mechanism apparently tied to the cytoskeleton. These pathways, which regulate tight junction solute permeability, are targets that produce epithelial barrier dysfunction in a variety of disease states. However, regulation of solute permeation across the junctional barrier may also represent a potential means to improve bioavailability of orally administered bioactive solutes. With permission, from the Annual Review of Physiology Volume 60, 1998, by Annual Reviews Inc. (http://www.annurev.org).

TEXT:
KEY WORDS: tight junctions, permeability, cytoskeleton, epithelia

INTRODUCTION

Solute transport across monolayers of columnar epithelia in vivo is often quantitatively astounding. The human intestine particularly exemplifies this. For example, consumption of meals and the subsequent osmotic equilibration of this intake in the proximal small intestine, coupled with endogenous secretions of hepatobiliary, gastroduodenal, pancreatic, and salivary origins, result in the delivery of approximately 9 liters of isosmotic fluid daily to this organ. Approximately 90[percent] of this volume is absorbed over the small intestine surface, which correcting for surface amplifications, including villous projections and microvilli on individual cells, has a surface area of 2 X 106 cm2. Because 1 liter of fluid that passes the ileocecal valve and enters the colon remains essentially isosmotic, it follows that a vast solute transport occurs across this epithelium. Not only must the intestinal epithelium support such solute transport to assure nutrition, but it must perform this function while simultaneously serving as a barrier restricting free diffusion of potentially noxious environmental molecules.

Historically, a simplified view of this absorptive process was that transcellular movement of nutrients and water via specific pumps, transporters, and channels would account for absorption, while an impermeable tight junction seal adjoining epithelial cells would provide for the requisite barrier function (the biophysical nature of lipid bilayers is such that passive movement of hydrophilic solutes across the transcellular pathway is highly restricted). However, it has become increasingly clear that transjunctional solute movement does occur, that it occurs in a regulated fashion, and that its regulation in certain states may be coupled to transcellular absorptive events. Thus epithelial solute transport and tight junction barrier function cannot be viewed as separate unrelated events, but rather as activities displaying coordinated interplay. This chapter discusses the principles of movement of hydrophilic solutes across tight junctions in qualitative terms. Although the focus is on the intestine, we draw on principles derived from a host of other natural and cultured epithelia.

METHODS TO ANALYZE TIGHT JUNCTION SOLUTE TRANSPORT

Methods to analyze tight junctions solute transport have recently been reviewed by Reuss (1) and Clausen (2). Because these methods are routinely and widely applied in cell biology and medical literature as assays of tight junction permeability, we discuss them here in general conceptual terms rather than in formalized biophysical terms. More biophysical explanations of these methods can be found in other reviews (1-3).

Additionally, our discussion centers largely on approaches that can be readily applied to epithelial monolayers and do not require specialized skills such as microelectrode techniques. Analyses of approaches utilizing intracellular recordings are well described elsewhere (1-3).

MEASUREMENTS OF RESISTANCE (DIRECT CURRENT)

Analysis of transepithelial resistance to passive ion flow relies on simplified equivalent circuit models of epithelia, such as those shown in Figure 1. Such circuit models view the epithelium as a parallel circuit consisting of paracellular and transcellular pathways. In turn, each of these pathways is composed of resistors in a series: the transcellular pathway as the apical and basolateral membranes in series, and the paracellular pathway as the tight junction and subjunctional intercellular space in series. Cable analyses afforded by microelectrode impalement approaches, which permit assessment of apical, basolateral, and shunt resistances, support the equivalent circuit model shown as a reasonable approximation of the epithelium (4, 5). Because transepithelial resistance of many natural or model epithelia (small intestine, gall bladder, or cell lines such as MDCK and CaCO-2, etc) is small (60-250 ohm cm2) relative to usual resistances of biomembranes (>1000 ohm cm2), variation in measured resistance values are often viewed in overly simplified terms as reflecting paracellular permeability. However this view is also simplified in general use: Because the tight junction is often rate limiting to paracellular solute movement, alterations in transepithelial resistance are often used as an index of tight junction permeability. Thus as used broadly in cell biological studies, a pulse of known amplitude is passed across the epithelium, the corresponding transepithelial voltage deflection is measured, and Ohm's law is used to calculate resistance, corrected for system and fluid resistance.

Although the above approach is useful in conjunction with others, several specific areas outlined below may potentially confound interpretation of such resistance measurements.

TRANSCELLULAR INFLUENCES ON TRANSEPITHELIAL RESISTANCE MAY BE
SUBSTANTIAL

Particularly in systems in which transepithelial resistance is greater than that outlined above, activation of membrane channels may lead to large changes in transepithelial resistance. For example, as neutrophils migrate across model intestinal epithelia, which exhibit baseline resistance values of 1,500 ohm cm2 (T84 cells) (6), alterations in transepithelial resistance occur that represent complex changes of resistance in both paracellular and transcellular pathways (7). Neutrophil migration across intercellular tight junctions, when occurring at high density (see below), alters junctional permeability as directly determined by analyses of flux of paracellular markers (below) and visualization of solute probes within the junction (8). However, neutrophils migrating across the epithelium also release 5'-AMP as a paracrine factor, which can be converted to adenosine by epithelial CD73. Adenosine is subsequently recognized by epithelial A2b receptors and, via a cAMP-dependent pathway, elicits electrogenic Cl secretion (9). Because this secretory response involves activation of apical Cl channels (and perhaps basolateral K channels) (10), a decrease in resistance due to alterations in transcellular resistance also occurs (7). This latter decrease in resistance, which is transcellular in origin, is several hundred ohm cm2. Other manipulations that activate these channels but do not change paracellular solute movement also produce substantial decreases in resistance (10). Thus as exemplified by this model, a decrease in transepithelial resistance by itself does not equate with altered paracellular solute transport.

CIRCUIT MODELS OF EPITHELIAL MONOLAYERS

The above paracellular and transcellular components of resistance can be modeled as an equivalent electrical circuit (Figure 1). Given the low cytoplasmic resistance, the transcellular resistance is largely contributed by the two rate-limiting barriers to passive ion flow in this pathway (the apical and basolateral membranes in series). The paracellular pathway (shunt pathway) resistance is parallel to the transcellular arm of the equivalent circuit and is often viewed as dominantly reflecting resistance of the intercellular tight junction because the tight junction appears rate limiting in the paracellular shunt pathway. However, even this view of the paracellular pathway is substantially oversimplified, as collapse of the subjunctional space, associated, for example, with an increase in cell volume, may substantially contribute to paracellular resistance, particularly if the junctional resistance is low (11). Collapse of the subjunctional intercellular space would also influence the resistance of the basolateral membrane of the transcellular pathway. Although the apical and basal portions of the membranes likely behave as simple series resistors, current exiting the lateral membrane could encounter an additional series resistance (the subjunctional intercellular space), and this additional resistance could vary depending on the length of intercellular space encountered. More quantitative analyses of these conceptual concerns in interpreting resistance measurements are well described elsewhere (3).

MONOLAYER EDGE EFFECTS

Work with epithelial sheets obtained from various species led investigators to realize that unless special precautions were taken, a significant component of passive paracellular ion flow could be related to artifactual damage of the edge associated with the crush induced by mounting mucosal sheets in the chamber. Such edge effects are usually neglected in studies of monolayers prepared from cultured intestinal epithelial cells, because monolayers are initially seeded on permeable supports that are pre-attached to a hemi-chamber, and thus edges are not crushed during chamber assembly.

However, the nature of the resistance seal between the edge of the chamber
and the monolayer under such conditions is not well understood. Visualization of stained monolayers suggests that (particularly when dealing with tissue culture--treated commercial supports) the monolayer extends 10 to 50 cell positions up the side of the chamber (J Madara, unpublished observations). Cells at the edge appear less columnar than those in the polarized monolayer. Furthermore, in selective surface biotinylation experiments, polarization of apically or basolaterally targeted membrane proteins appears to be significantly more complete if the
edge of the monolayer is not included in the post-labeling lysate (12). Such observations suggest that either edge-related leakage of biotin and/or significant attenuation of the polarized phenotype (consistent with the morphologic appearance of the edge) are artifacts associated with such edges. The growth of the epithelial monolayer a short distance along the edge of the well appears, by electrical assays, to provide an adequate electrical seal that does not influence electrical readings to a substantial degree (for example, altering the edge/surface ratio by using chamber-mounted filters varying in dimension appears to yield similar resistance values, consistent with the absence of significant edge effects; J Madara, unpublished observations).

MEASUREMENTS OF IMPEDANCE (ALTERNATING CURRENT)

If membrane capacitance is accounted for in an equivalent circuit model such as that shown in Figure 1, use of alternating current may permit more sensitive assignment of resistance values to parameters such as the tight junction and subjunctional paracellular space (2, 11). Because current interacts with such circuits in a frequency-dependent manner that can be resolved mathematically, accurate measurement of even low-resistance tight junction components should be possible. A major limitation of this approach, however, is to design a circuit model that accurately represents the monolayer studied, and it is difficult to do this without major uncertainties related to various problems, some of which are mentioned above. One approach to this problem is to subject a proposed circuit model and the impedance data obtained to an independent approach such as morphology (11). For example, if (a) substantial increases in basolateral membrane area (defined morphologically) correspond to expected increases in
capacitance, if (b) alterations in junctional structure and solute flux correlate with changes in junctional resistance, and if (c) similar correlations are found with other components of the circuit, then the circuit model is considered a reasonable simplification of the tissue in hand (13). In essence, such approaches (although producing highly reproducible values) will yield data that are only as reliable as the proposed equivalent circuit is reflective of the epithelium studied.

FLUX

When morphologically detectable tracers, which can be immobilized after tissue exposure, were utilized to examine the permeability of epithelia, these tracers were impeded from entering the paracellular space from the apical bathing solution (14). When applied basolaterally, such tracers

freely permeated the subjunctional intercellular spaces but were again blocked from entering the lumen by the apical tight junction. A smaller undecapeptide, which can be similarly immobilized and visualized, and divalent cations, which can be precipitated and visualized, provided evidence that the tight junction was the rate-limiting barrier to passive transepithelial flux of inert solutes (14). Typically, only cruder forms of injury will result in detectable leak of macromolecules across tight junctions, whereas some movement of small peptides across tight junctions can be induced by physiological stimuli (Figure 2). Corresponding studies of transepithelial flux of hydrophilic solutes of varying hydrodynamic radii indicate that tight junctions are size selective (15). Thus analyses of transepithelial flux of inert solutes such as mannitol, inulin, and dextrans are widely utilized to determine the permeability characteristics of tight junctions (15, 16).

Analyses of solute movement across epithelial and endothelial tight junctions is often reported as a percent of tracer, which moves from one side of the epithelium to the other, rather than as an actual flux, which takes into account activity and is reported in units of mass area-1 time-1. A general consideration of these approaches is useful to highlight the pitfall of percent tracer transfer measurements as they are now widely applied. If one places trace inulin (5000 Mr; 11.5 A radius) above a commercially available permeable support [e.g. a Costar device with an insert of a polycarbonate filter having 5 mm pores and with reservoir volumes as would occur in a 24-well plate (1 ml basolaterally and 200 ul apically)], equilibration will occur over a period of 2 h. In numerous publications this approach has been used in the presence and absence of plated cells and, if the cell monolayer retards such equilibration substantially (>90[percent]), it is concluded that a biophysically confluent monolayer is formed. However, as cell membranes have very restricted permeability to such tracers, the degree to which cells cover the surface area of the filter is the same degree to which the pathway available for diffusion from one chamber to another becomes restricted. Thus if fibroblasts, which do not form intercellular tight junctions, are grown as a monolayer in which the cells closely abut, the available open paracellular space for diffusion easily can be <95[percent] of the area available on a blank filter. Judging by this criterion then, investigators could erroneously conclude that fibroblasts exhibit functional intercellular tight junctions. More reasonable evidence of biophysically confluent monolayers would be flux rates compatible with confluency (in the range of nmoles-1 cm-2 for inulin) and size selectivity, including impermeability to macromolecules (confirmed by non-permeability at 18[degree]C, a temperature at which transcytosis is blocked). In general, flux analyses across biophysically confluent monolayers for periods of 1 h result in transfer of a negligible percent of net tracer, and such experiments are ideally performed under conditions where both reservoirs are actively stirred in order that activities are uniform in the bathing solutions.

Consideration of the relationship between flux and resistance provides insight into which test of permeability might best apply to a given cultured epithelial monolayer. Routine analyses of resistance to passive ion flow essentially regard the tight junctions of single cells as individual resistances in parallel. Solutions for such parallel circuits reveal that components of low resistance can dominate the net resistance of such a circuit, even when these components are present at low frequency (Figure 3). In contrast, flux measurements are essentially the sum of fluxes across all junctional pathways (15, 16). As a result, the relationship between transepithelial resistance and solute flux is nonlinear. Given these considerations, one finds that, particularly at values of several hundred ohm per cm2 and above, very small increments in junctional permeability may produce large decreases in resistance. Conversely, at low-resistance values (<200 ohm cm2), as routinely measured by direct current techniques, relatively large changes in transjunctional flux of hydrophilic solutes will often be associated with very modest changes in transepithelial resistance (7). An example of this relationship between resistance and flux of a paracellular marker is shown in Figure 4. In low-resistance states, measurement of transepithelial resistance may have exaggerated errors in systems now commonly applied to cultured monolayers. For example, it is usual in the cell biology literature to measure transepithelial resistance of monolayers in 24-well systems plated on permeable supports. If the resistances of monolayers are high (<500 ohm cm2), current densities are likely to be uniform at the monolayer surface even with the low reservoir volumes (200 ml) on the apical side and with the short distances from apical bridges to the monolayer surface. In contrast, low-resistance monolayers appear to have significant differences in readings related to the positioning of the apical bridges, and such variances can influence reproducibility of resistance values. For these reasons, it is helpful, when characterizing new monolayer systems, to rely on resistance and flux values of symmetrical Ussing chambers adapted for cultured cells. These chambers have the advantages of having fixed agar bridges that are distant from the monolayer surfaces and stirring of the solutions (the latter advantage is key for flux analyses). Measurements from simpler systems can then be judged against this standard.

GENERAL CORRELATES BETWEEN TIGHT JUNCTION STRUCTURE AND SOLUTE PERMEABILITY

Claude & Goodenough (18) first recognized a general positive relationship between resistance to passive ion flow and numbers of tight junction strands as revealed in freeze fracture replicas. Claude subsequently reported that as the numbers of tight junction strands increased, the transjunctional resistance values increased exponentially (19)--a finding that led to the suggestion that junctional pores fluctuate between closed and open states. Recently, Balda et al provided further indirect evidence that junctional pores (i.e. the sites of permeation in the otherwise tight seal of the junctional strand) are gated (20). This idea was utilized to explain data obtained from epithelia expressing COOH-terminal truncations of occludin, which suggested that in some states of regulation, junctional permeability to hydrophilic solutes could be enhanced in the absence of a change in junctional resistance. Thus it was suggested that while flux represents net movement of solute across a junction with several pores in series, resistance measurements are detecting a continuous series of pores that are synchronously in the open state across the width of the junction (Figure 5). Although the general relationship between strand number and resistance appears valid, it is now clear that this relationship (a) is likely complicated by considerations such as open probabilities of the permeable pores and (b) is further confounded by cell heterogeneity. For example, given the foregoing discussion it is clear that if an epithelial monolayer is composed of cells with two differing tight junctions, the most permeable phenotype will dominate the paracellular permeability characteristics of the overall monolayer (as judged by electrical assays) even if that phenotype is infrequent (Figure 3). Thus monolayers with two or more junctional phenotypes related to differing positions in the cell cycle in a clonal cell line might have junction permeability heterogeneity. Such features complicate the dissection of general structure/function correlates, although analyses of structural features in such heterogeneous systems using principles of circuit analyses support the relationship suggested by Claude & Goodenough.

Junctional strands, the sites of close membrane-membrane apposition (called kisses) within the tight junction, are the location of the transmembrane protein occludin. Recently, it was shown that a synthetic peptide corresponding to the extracellular domain of occludin is capable of enhancing tight junction permeability, thus verifying that occludin is likely involved in establishing the seal at the sites of junctional strands (22). Occludin, in turn, is linked to peripheral membrane proteins such as ZO-1, ZO-2, and cingulin. The tight junction is also enriched in cytoplasmic/membrane-associated proteins that typically control either vesicular trafficking (rab 13) or signal transduction (src). These specific junction-associated proteins are described in detail by L Mitic & JM Anderson in this volume. In general, the specific contributions of these proteins to junctional permeability is just beginning to be understood, and although evidence of events such as phosphorylation of specific junction-associated proteins are associated with alterations in junctional permeability under specific conditions, it is not yet clear if such changes represent cause-effect relationships.

REGULATION OF TIGHT JUNCTION SOLUTE TRANSPORT

CYTOSKELETAL CONTRIBUTIONS

Aside from the potential for junctional permeability regulation via modulation of the specific junction-associated proteins (see above and L Mitic & JM Anderson, this volume), the influence of the actin-myosin II-based cytoskeleton also exists. Numerous second messenger pathways have been shown capable of influencing perijunctional cytoskeletal organization in concert with changes in junctional permeability (21, 23, 24). However, the changes often vary between specific cell types, and the agonists used to establish this principle were often not physiological.

The perijunctional actin-myosin II ring encircles the apical pole of polarized columnar epithelial cells, and the major interface of this ring with the lateral membrane occurs just below the tight junction at the adherens junction. Given that lateral tension appears capable of

influencing tight junctions (25), it has been suggested that tension within the perijunctional actin-myosin II ring may influence solute permeation (24-27). The actin and myosin II filament alignment within the ring allows for contraction and, in fact, the ability of this ring to contract in isolated brush borders of enterocytes was demonstrated some 20 years ago (28). However, F-actin microfilaments projecting from the ring also interface at kiss sites within the tight junction (29) (Figure 6), thus allowing for more direct interactions between the rate-limiting permeability barrier within the junction and the F-actin-based cytoskeleton.

Control of cytoskeletal events by small GTPases rho, rac, and Cdc42 at the leading edge of serum-starved and repleted fibroblasts points to a role for these proteins in the signaling cascades that control dynamic F-actin rearrangement (30). The role of these small G proteins in polarized columnar epithelial cells has been less well studied because the tools used, including a %%bacterial%%-derived toxin (C3) that selectively ribosylates rho proteins and uncouples them from their effectors, are often difficult to apply to polarized cells. For example, the C3 toxin does not permeate membranes and thus must be microinjected. A recent strategy utilizing a chimeric toxin, which included a binding subunit that recognizes a cell surface receptor, has permitted uniform intracellular delivery of C3 to polarized monolayers of columnar epithelia (31). In these cells, the dominant influence of rho ribosylation is solation of apical F-actin, including that contained within the F-actin ring. These effects are in parallel with the loss of ZO-1 from the membrane at the site of the tight junction without effects on the distribution of underlying E-cadherin. In parallel, tight junction permeation of hydrophilic solutes occurs. Such data suggest that these crucial cytoskeletal regulatory proteins have a major influence on the structure of the perijunctional cytoskeleton in static polarized confluent monolayers (while having less influence on basal F-actin). Interestingly, the effectors of rho include kinase systems that influence actin-myosin interactions as well as F-actin interactions with the plasma membrane (32).

Evidence supporting physiological agonists that influence junctional permeation via probable effects on the cytoskeleton has also been found. For example, in response to histamine, the endothelial cells retract from each other and become round due to cytoskeletal tension brought about by phosphorylation of myosin light chain (33). Similarly, activation of the receptor for antidiuretic hormone by its physiological ligand produces a Ca2+ signal that is coupled to phosphorylation of myosin light chain and enhanced solute permeability of hepatocyte tight junctions (33). Lastly, activation of enterocyte Na+-glucose cotransport similarly alters tight junction solute transport in association with condensation of the perijunctional actin-myosin II ring (11, 13). Overexpression of the transport protein (SGLT1) in cultured human intestinal epithelial cell lines permits recovery of this physiologically mediated alteration in junctional solute permeability and is also coupled to enhanced myosin light chain phosphorylation (J Turner, JL Madara, manuscript in preparation).

Other examples of physiological regulation of junctional solute permeability by physiological signals that are even less well understood include epidermal growth factor (34), hepatocyte growth factor (35), interferon-gamma (36), and insulin (37). The last two agonists are also coupled with alterations in perijunctional actin organization but occur over a much longer time course and appear to require new protein synthesis.

PATHOBIOLOGY OF TIGHT JUNCTION PERMEABILITY TO SOLUTES

Several disease-associated states have a pathobiology that effectively alters normal solute permeability of intercellular tight junctions. For example, a toxin derived from Vibrio cholera, termed ZO toxin or ZOT, appears to influence junctional solute permeation by influencing one of the second messenger pathways (PKC) previously shown to influence junctional permeation in specific cell types (38). Similarly, toxins derived from Clostridium difficile (Toxins A and B) cause profound alterations in tight junction solute permeability of enterocytes and do so in association with solation of the F-actin microfilaments of the perijunctional actin-myosin II ring (39, 40). Rho and the related proteins rac and Cdc42 are now recognized as targets for these latter toxins, which act by glucosylation and, similar to C3 toxin, uncouple these proteins from their effectors (32).

Physiological regulation of tight junction solute transport may also influence tissue pathophysiology in disease states. As discussed above, activation of SGLT1 by luminal glucose alters the permeability of enterocyte tight junctions such that small solutes, potentially including antigens, can cross into the subepithelial space more efficiently. Castro and colleagues (41) have recently shown that intestinal anaphylaxis due to oral challenge with antigen is markedly influenced by the inclusion of glucose with the orally administered antigen. Because inclusion of other sugars, which do not activate SGLT1 (or inclusion of SGLT1 inhibitors), ablates this response, it appears that this form of physiological regulation of junctional solute transport has pathophysiological consequences in certain settings.

Lastly, cell-cell interactions that commonly occur in pathological circumstances can also influence junctional solute permeability. For example, migration of neutrophils across epithelial or endothelial surfaces induces a reversible increase in tight junction permeability, presumably the direct consequence of perturbation of the structural barrier (42). Although the mechanisms underlying such alterations are not clear, studies performed on endothelial monolayers suggest that neutrophil contact with this cell type promotes a cytosolic Ca2+ signal that permissively opens junctions via a cytoskeleton-dependent event (43). In this view, the endothelial cell behaves cooperatively with the neutrophil in the transmigration event, and control of junctional permeation appears directly and actively regulated by the endothelial cell. It is not clear if similar events also occur in epithelia.

TIGHT JUNCTION SOLUTE PERMEATION AS A TARGET FOR DRUG DELIVERY

Better understanding of the mechanisms by which solute movement across tight junctions is regulated is of potential pharmacological significance. Orally administered reagents sometimes contain so-called barrier breakers--agents that transiently disrupt the epithelial barrier by nonspecific means (i.e. these epithelia possess attributes that permit rapid repair by flattening, spreading, and migration of individual epithelial cells). Using the same basic principle, junctional permeability can be transiently modified by more physiological means. Thus glucose-elicited activation of SGLT1 causes a reversible alteration in junctional solute permeability that has been utilized as a means for improving oral bioavailability of peptides, such as somatostatin analogues, which have been engineered to resist hepatic degradation by substitution of D-amino acids (44). Those approaches that build on understanding the mechanisms by which tight junction solute permeation is naturally regulated may provide insights into simple everyday problems, including improved bioavailability of orally administered drugs.

Added material

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Figure 1 Equivalent circuit model of an epithelium. Two polarized epithelial cells (rectangles) are joined apically by a dark line representing the circumferential continuous tight junction. The circuit contains two parallel resistive arms. The paracellular arm consists of a tight junction resistance (Rtj) in series with a subjunctional lateral space resistance (Rsubjunctional). Although the resistance of the subjunctional space is often considered minimal in comparison with that of the tight junction, under certain circumstances (where Rtj is low and/or the paracellular space is collapsed as it is when epithelial cells swell), Rsubjunctional may even be dominant. The transcellular arm of the circuit consists of an apical membrane resistance (Ra) in series with a basolateral membrane resistance (Rbl). Rbl will also be distributed, meaning that portions of the current will exit cells along the lateral membrane and thus also be in series with portions of Rsubjunctional.

Figure 2 Electron micrographs of tight junctions of small intestinal absorptive cells that respond to activation of apical membrane Na+-glucose cotransport with the appearance of intrajunctional dilatations and enhanced junctional permeability (see text). (A) Leakage of an 11-amino acid peptide, which can be fixed in place and localized by development of a reaction product into a dilatation, is indicated (arrowhead), but as shown in (B), a macromolecule (horseradish peroxidase) remains excluded from such dilatations (x 45,000).

Figure 3 Model of epithelial tight junctions as a circuit of parallel resistors. To consider how total circuit resistance is influenced by a subpopulation of junctions of low resistance, one can substitute resistance values and frequencies for individual components (assuming there are 10 junctions each for R1, R2, and R3, and 70 junctions have the Rn value). In a uniform population of 100 junctions, each having a resistance of 10,000 ohm, the RT is 100 ohm. However if the 10 junctions of the R1 variety have a resistance of 1,000 ohm, RT now approaches half the former value (50 ohm). Such considerations reinforce how minor populations of junctions can inordinately influence overall paracellular resistance and in so doing, confound structure-function analyses in a heterogeneous monolayer.

Figure 4 Example of the relationship between flux of a small inert paracellular marker (mannitol, hydrodynamic radius 3.6 A) and transepithelial resistance during maturation of a polarized columnar epithelial monolayer plated at confluent density. At low-resistance values, flux appears a more reliable index of changes in junctional permeation. At high-resistance values, flux does not sensitively measure the very subtle increments in monolayer resistance that might be related to increased resistance in a minor (previously lower resistance) subpopulation of junctions that dominate the electrical characteristics of the monolayer (see text).

Figure 5 Diagrammatic representation of potential means of dissociation of resistance values from measured solute flux across tight junction strands, as proposed by Balda et al (20). The three open pores shown permit solute diffusion from the apical to subjunctional compartment and because a continuous channel is formed across the resistive component of the tight junction, an electrically detectable channel would result. However, if the pores open in a dysynchronous fashion, solute diffusion (which does not require temporal continuity of the transjunctional pathway) might dissociate from the electrical measurement (which would require temporal continuity of the transjunctional pathway).

Figure 6 Electron micrograph (left) and labeled sketch (right) of naked cytoskeleton in a zone of an ideally sectioned absorptive-cell tight junction. Electron-dense plaques intimately associate with intrajunctional kisses on one side and with cytoskeletal elements on the other. Specifically, in sections unlabeled with S1 actin probe, such cytoskeletal elements appear to be microfilaments (not shown), and in sections labeled with S1 (shown), such microfilaments are shown to be actin microfilaments by characteristic arrowhead label due to S1-actin association. x 115,000.

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8/7/110 (Item 1 from file: 103)
DIALOG(R)File 103:Energy SciTec

01829279 EDB-86-153158
Title: Monosaccharide precursor of Echerichia coli lipid A has the ability to induce %%%tumor%%%-%%%cytotoxic%%% %%%factor%%% production by a murine macrophage-like cell line, J774.1
Author(s): Amano, F.; Nishijima, M.; Akamatsu, Y.
Affiliation: National Institute of Health, Tokyo, Japan
Source: J. Immunol. (United States) v 136:11. Coden: JOIMA
Publication Date: 1 Jun %%%1986%%%
p 4122-4127
Language: English
Abstract: A monosaccharide precursor of Escherichia coli lipid A, designated lipid X, which is a diacylglucosamine 1-phosphate with ..beta..-hydroxymyristoyl groups at positions 2 and 3, was shown to have the ability to induce the production of tumor necrosis factor (TNF)-like %%%tumor%%%-%%%cytotoxic%%% %%%factor%%% by a murine macrophage-like cell line, J774.1. This cytotoxic factor was released from J774.1 cells grown in the presence of lipid X and related compounds, and it was assayed as to its lytic activity against (/sup 3/H)thymidine-labeled L929 cells. Dose-response studies revealed that lipid X induced the production of smaller amounts of the %%%tumor%%%-%%%cytotoxic%%% %%%factor%%% than LPS at low concentrations, but it induced that of considerable amounts at and over 1 ..mu..g/ml. Elimination of 1-phosphate or 3-O-..beta..-hydroxymyristoyl group from lipid X completely prevented the induction of producing this factor by the macrophages. Therefore, it is suggested that both 1-phosphate and 3-O-..beta..-hydroxymyristoyl groups are essential for the biologic activity of lipid X, as to the induction of the %%%tumor%%%-%%%cytotoxic%%% %%%factor%%% production in the macrophages.

8/7/111 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

12933389 PASCAL No.: 97-0205383
Hepatocyte growth factor/%%%scatter%%% %%%factor%%% promotes adhesion of lymphoma cells to extracellular matrix molecules via alpha SUB 4 beta SUB 1 and alpha SUB 5 beta SUB 1 integrins
WEIMAR I S; DE JONG D; MULLER E J; NAKAMURA T; VAN GORP J M H H; DE GAST G C; GERRITSEN W R
Department of Immunology, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Biochemistry, Biomedical Research Center, Osaka University Medical School, Japan; Department of Pathology, University Hospital, Utrecht, Netherlands; Department of Hematology, University Hospital, Utrecht, Netherlands; Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands
Journal: Blood, %%%1997%%%, 89 (3) 990-1000
ISSN: 0006-4971 Availability: INIST-3178; 354000063323820280
No. of Refs.: 76 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
Hepatocyte growth factor (HGF)/%%%scatter%%% %%%factor%%% (SF) is the ligand for a tyrosine kinase cell surface receptor encoded by the MET protooncogene (c-MET). HGF/SF can induce proliferation and motility in epithelial cells and promotes invasion of carcinoma cells and NIH3T3 fibroblasts transfected with both HGF/SF and c-MET genes. Our results show that HGF/ SF and c-MET also play a role in adhesion and invasion of human lymphoma cells. c-MET mRNA is expressed in hemopoietic cells, such as hemopoietic progenitor cells (CD34 SUP + cells) in bone marrow (BM) and mobilized peripheral blood, immature B cells in cord blood and BM, and germinal center B-centroblasts. In normal peripheral blood B cells, which are c-MET SUP - , c-MET expression was induced by PMA, ConA, HGF/ SF, and Epstein-Barr virus (EBV) %%%infection%%%. Using immunohistochemistry, we detected c-MET on the cell surface of large activated centroblasts in lymph nodes from patients with B-non-Hodgkin's lymphoma and Hodgkin's disease. In the latter group, c-MET expression correlated well with the presence of EBV. Because HGF/SF and c-MET promote metastasis of carcinoma cells, we studied the effects of c-MET stimulation by HGF/SF of B-lymphoma cells on properties relevant for metastasis, ie, adhesion, migration, and invasion. HGF/SF stimulated adhesion of the c-MET SUP + B-cell lines to the extracellular matrix molecules fibronectin (FN) and collagen (CN) in a dose dependent manner. However, adhesion to laminin was not affected by HGF/SF.
Adhesion to FN was mediated by beta SUB 1 -integrins alpha SUB 4 beta SUB 1 (VLA4) and alpha SUB 5 beta SUB 1 (VLA5) since blocking antibodies against beta SUB 1 - (CD29), alpha SUB 4 -(CD49d), or alpha SUB 5 - (CD49e) integrin subunits, completely reversed the effect of HGF/SF. Furthermore, HGF/SF induced adhesion was abrogated by addition of genistein, which blocks protein tyrosine kinases, including c-MET. Addition of HGF/SF resulted in a sixfold increase in migration of c-MET B-lymphoma cells through Matrigel, compared to medium alone. In rat fibroblast cultures, HGF/SF doubled the number of c-MET SUP + B-lymphoma cells that invaded the fibroblast monolayer. In these adhesion, migration and invasion assays HGF/SF had no effect on c-MET SUP - cell lines. In conclusion, c-MET is expressed or can be induced on immature, activated, and certain malignant B cells. HGF/SF increased adhesion of c-MET SUP + B-lymphoma cells to FN and CN, mediated via beta SUB 1 -integrins alpha SUB 4 beta SUB 1 and alpha SUB 4 beta SUB 1 , and furthermore promoted migration and invasion.

8/7/112 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08069481 93136665 PMID: 8380735
Structure, biosynthesis and biochemical properties of the HGF receptor in normal and malignant cells.
Comoglio PM
Dept. of Biomedical Sciences and Oncology, University of Torino, School of Medicine, Italy.
EXS (SWITZERLAND) %%%1993%%%, 65 p131-65, Journal Code: BFZ
Languages: ENGLISH
Document type: Journal Article; Review; Review, Academic
Record type: Completed
Hepatocyte Growth Factor (HGF) and %%%Scatter%%% %%%Factor%%% (SF) are identical glycoproteins secreted by cells of mesodermal origin. The factor has several activities on epithelial cells, including mitogenesis, dissociation of epithelial sheets, stimulation of cell motility, and promotion of matrix invasion. HGF is the ligand for p190MET, the receptor tyrosine kinase encoded by the MET proto-oncogene. This was proved by HGF binding to immunopurified p190MET, chemical cross-linking of radiolabelled ligand, HGF-induced tyrosine phosphorylation of p190MET, and reconstitution of high-affinity binding sites for HGF into insect cells %%%infected%%% with a recombinant baculovirus carrying the human MET cDNA. p190MET is a 190 kDa heterodimer of two (alpha beta) disulfide-linked protein subunits.

The alpha subunit is heavily glycosylated and extracellular. The beta subunit bears an extracellular portion involved in ligand binding, a membrane spanning segment and a cytoplasmic tyrosine kinase domain with phosphorylation sites regulating its activity. Both subunits originate from glycosylation and proteolytic cleavage of a common precursor of 170 kDa. Alternative post-transcriptional processing originates two truncated Met proteins, endowed with ligand binding activity, lacking the cytoplasmic kinase domain of the beta subunit. One form is soluble and released from the cells. HGF binding triggers tyrosine autophosphorylation of the receptor beta subunit in intact cells. Autophosphorylation upregulates the kinase activity of the receptor, increasing the Vmax of the phosphotransfer reaction. The major phosphorylation site has been mapped to Tyr1235. Negative regulation of the receptor kinase activity occurs through distinguishable pathways involving protein kinase C activation or increase in the intracellular Ca2+ concentration. Both lead to the serine phosphorylation of a unique phosphopeptide of the receptor and to a decrease in its kinase activity. Receptor autophosphorylation also triggers the signal transduction pathways inside the target cells. The phosphorylated receptor associates ras GAP, phospholipase C-gamma, and src-related tyrosine kinase in vitro; Phosphatidylinositol 3-kinase, in vitro and in vivo, indicating that the generation of the D-3 phosphorylated inositol lipids is involved in effecting the motility and/or the growth response to HGF. The p190MET HGF receptor is expressed in several epithelial tissues and it is often overexpressed in neoplastic cells. In some tumors of the gastrointestinal tract the Met tyrosine kinase is constitutively activated, either by overexpression of the amplified MET oncogene or by lack of cleavage of the receptor precursor, due to defective post-translational processing. (178 Refs.)
Record Date Created: 19930219

8/7/113 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05493255 90109933 PMID: 2558106
Protein factors which regulate cell motility.
Rosen EM; Goldberg ID
Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut 06510.
In vitro cellular & developmental biology (UNITED STATES) Dec %%%1989%%%, 25 (12) p1079-87, ISSN 0883-8364 Journal Code: HEQ
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
Cell motility (i.e., movement) is an essential component of normal development, inflammation, tissue repair, angiogenesis, and tumor invasion. Various molecules can affect the motility and positioning of mammalian cells, including peptide growth factors, (e.g., EGF, PDGF, TGF-beta), substrate-adhesion molecules (e.g., fibronectin, laminin), cell adhesion molecules (CAMs), and metalloproteinases. Recent studies have demonstrated
a group of motility-stimulating proteins which do not appear to fit into any of the above categories. Examples include: 1) %%%scatter%%% %%%factor%%% (SF), a mesenchymal cell-derived protein which causes
contiguous sheets of epithelium to separate into individual cells and stimulates the migration of epithelial as well as vascular endothelial cells; 2) autocrine motility factor (AMF), a tumor cell-derived protein which stimulates migration of the producer cells; and 3) migration-stimulating factor (MSF), a protein produced by fetal and cancer patient fibroblasts which stimulates penetration of three-dimensional collagen gels by non-producing adult fibroblasts. SF, AMF, and MSF are soluble and heat labile proteins with Mr of 77, 55, and 70 kd by SDS-PAGE, respectively, and may be members of a new class of cell-specific regulators of motility. Their physiologic functions have not been established, but available data suggest that they may be involved in fetal development and/or tissue repair. (97 Refs.)
Record Date Created: 19900222

8/7/114 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

131237965 CA: 131(18)237965e PATENT
Tumor cytotoxic factor-II as preventives and/or remedies for sepsis
INVENTOR(AUTHOR): Tani, Tohru; Kondo, Hiroyuki
LOCATION: Japan,
ASSIGNEE: Snow Brand Milk Products Co., Ltd.
PATENT: PCT International ; WO 9947155 A1 DATE: 19990923
APPLICATION: WO 99JP1373 (19990319) *JP 9870914 (19980319)
PAGES: 15 pp. CODEN: PIXXD2 LANGUAGE: Japanese CLASS: A61K-038/17A
DESIGNATED COUNTRIES: AU; CA; KR; NZ; US; ZA DESIGNATED REGIONAL: AT; BE
; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA201006 Pharmacology
CA263XXX Pharmaceuticals
IDENTIFIERS: tumor cytotoxic factor II sepsis
DESCRIPTORS:
Drug delivery systems...
injections, freeze-dried; tumor cytotoxic factor-II as remedies for sepsis
Nutrition,animal...
parenteral, total, sepsis from; tumor cytotoxic factor-II as remedies for sepsis
AIDS(disease)... Burn... Chemotherapy... Infection... Neoplasm... Radiotherapy... Surgery...
sepsis from; tumor cytotoxic factor-II as remedies for sepsis
Cytokines... Lymphokines... Sepsis...
tumor cytotoxic factor-II as remedies for sepsis

8/7/115 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

129221211 CA: 129(17)221211d PATENT
Preventive and/or therapeutic agent for cachexia
INVENTOR(AUTHOR): Kojiro, Masamichi; Yano, Hirohisa; Iemura, Akihiro
LOCATION: Japan,
ASSIGNEE: Snow Brand Milk Products Co., Ltd.
PATENT: PCT International ; WO 9841230 A1 DATE: 19980924
APPLICATION: WO 98JP999 (19980311) *JP 9782162 (19970314)
PAGES: 16 pp. CODEN: PIXXD2 LANGUAGE: Japanese CLASS: A61K-038/22A
DESIGNATED COUNTRIES: AU; CA; KR; US DESIGNATED REGIONAL: AT; BE; CH; DE
; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA263006 Pharmaceuticals
CA201XXX Pharmacology
CA215XXX Immunochemistry
IDENTIFIERS: cachexia tumor cytotoxic factor II
DESCRIPTORS:
AIDS(disease)... Burn... Chemotherapy... Connective tissue diseases... Diabetes mellitus... Endotoxemia... Heart diseases... Infection... Radiotherapy... Shock(circulatory collapse)... Surgery... Tumors(animal)...
cachexia caused by; preventive and/or therapeutic agent contg. tumor cytotoxic factor II for cachexia
Injections(drug delivery systems)...
freeze-dried; preventive and/or therapeutic agent contg. tumor cytotoxic factor II for cachexia
Organ(animal)...
inflammation, cachexia caused by; preventive and/or therapeutic agent contg. tumor cytotoxic factor II for cachexia
Freeze-dried drug delivery systems...
injections; preventive and/or therapeutic agent contg. tumor cytotoxic factor II for cachexia
Inflammation...
organ, cachexia caused by; preventive and/or therapeutic agent contg. tumor cytotoxic factor II for cachexia
Antitumor agents... Cachexia... Injection solutions(drug delivery systems)
...
preventive and/or therapeutic agent contg. tumor cytotoxic factor II for cachexia
Lymphokines...
tumor cytotoxic factor II; preventive and/or therapeutic agent contg. tumor cytotoxic factor II for cachexia

8/7/116 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

128136501 CA: 128(12)136501h PATENT
Treatment of Kaposi's sarcoma by inhibition of scatter factor
INVENTOR(AUTHOR): Nickoloff, Brian J.; Naidu, Yahti M.; Rosen, Eliot M.;
Polverini, Peter J.
LOCATION: USA
ASSIGNEE: Regents of the University of Michigan
PATENT: United States ; US 5707624 A DATE: 19980113
APPLICATION: US 253728 (19940603)
PAGES: 24 pp. CODEN: USXXAM LANGUAGE: English CLASS:
424158100;
A61K-039/395A
SECTION:
CA201006 Pharmacology
CA202XXX Mammalian Hormones
CA214XXX Mammalian Pathological Biochemistry
CA215XXX Immunochemistry
IDENTIFIERS: scatter factor inhibition Kaposi sarcoma antitumor, antibody
scatter factor Kaposi sarcoma antitumor, receptor met antibody Kaposi sarcoma antitumor, ligand met receptor Kaposi sarcoma antitumor
DESCRIPTORS:
Interleukin 6...
and anti-IL-6 antibodies; scatter factor inhibition for treatment of Kaposi's sarcoma
Smooth muscle...
artery, cells; scatter factor inhibition for treatment of Kaposi's sarcoma
T cell(lymphocyte)...
HTLV-II-infected; scatter factor inhibition for treatment of Kaposi's sarcoma
Kaposi's sarcoma...
inhibitors; scatter factor inhibition for treatment of Kaposi's sarcoma
Sarcoma inhibitors...
Kaposi's; scatter factor inhibition for treatment of Kaposi's sarcoma
Angiogenesis inhibitors... Angiogenesis... CD80(antigen)... Hepatocyte growth factor receptors... Hepatocyte growth factor... ICAM-1(cell adhesion molecule)... Interferon .gamma.... Interleukin 1.beta.... Interleukin 10... Interleukin 8... mRNA... Phenotypes... T cell proliferation... Transforming growth factor .alpha.... Transforming growth factors .beta.... Vascular endothelium... VCAM-1(cell adhesion molecule)...
scatter factor inhibition for treatment of Kaposi's sarcoma
Superantigens...
SEB-10; scatter factor inhibition for treatment of Kaposi's sarcoma
Artery...
smooth muscle cells; scatter factor inhibition for treatment of Kaposi's sarcoma
Human T-lymphotropic virus 2...
T-cell infected with; scatter factor inhibition for treatment of Kaposi's sarcoma
Ligands...
to c-met receptor; scatter factor inhibition for treatment of Kaposi's sarcoma
Antibodies...
to scatter factor and other mols.; scatter factor inhibition for treatment of Kaposi's sarcoma
Neutralizing antibodies...
to scatter factor; scatter factor inhibition for treatment of Kaposi's sarcoma
CAS REGISTRY NUMBERS:
106956-32-5 antibodies to; scatter factor inhibition for treatment of Kaposi's sarcoma
9067-75-8 83869-56-1 scatter factor inhibition for treatment of Kaposi's sarcoma

8/7/117 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

126236827 CA: 126(18)236827w JOURNAL
Inactivation of retinoblastoma family proteins by SV40 T antigen results in creation of a hepatocyte growth factor/scatter factor autocrine loop associated with an epithelial-fibroblastoid conversion and invasiveness
AUTHOR(S): Martel, Cecile; Harper, Francis; Cereghini, Silvia; Noe, Veerle; Mareel, Marc; Cremisi, Chantal
LOCATION: CJF 94-02, Universite Rene Descartes, 006, Paris, Fr.
JOURNAL: Cell Growth Differ. DATE: 1997 VOLUME: 8 NUMBER: 2
PAGES:
165-178 CODEN: CGDIE7 ISSN: 1044-9523 LANGUAGE: English
PUBLISHER:
American Association for Cancer Research
SECTION:
CA214001 Mammalian Pathological Biochemistry
CA202XXX Mammalian Hormones
CA210XXX MICROBIAL, ALGAL, AND FUNGAL BIOCHEMISTRY
IDENTIFIERS: retinoblastoma protein SV40 T antigen, epithelial transformation scatter factor SV40 antigen, hepatocyte growth factor T antigen transformation
DESCRIPTORS:
Tumors(animal)...
epithelium; inactivation of retinoblastoma family proteins by SV40 T antigen results in scatter factor autocrine loop assocd. with epithelial-fibroblastoid conversion and invasiveness
Cell differentiation... Cell morphology... Hepatocyte growth factor... Large T antigen... MDCK cell... Rb protein... Simian virus 40...
Transformation(neoplastic)...
inactivation of retinoblastoma family proteins by SV40 T antigen results in scatter factor autocrine loop assocd. with epithelial-fibroblastoid conversion and invasiveness
Tumors(animal)...
mesenchymal; inactivation of retinoblastoma family proteins by SV40 T antigen results in scatter factor autocrine loop assocd. with epithelial-fibroblastoid conversion and invasiveness
Epithelium...
tumor; inactivation of retinoblastoma family proteins by SV40 T antigen results in scatter factor autocrine loop assocd. with epithelial-fibroblastoid conversion and invasiveness
Mesenchyme...
tumors; inactivation of retinoblastoma family proteins by SV40 T antigen results in scatter factor autocrine loop assocd. with epithelial-fibroblastoid conversion and invasiveness
Transcription factors...
vHNF1; inactivation of retinoblastoma family proteins by SV40 T antigen results in scatter factor autocrine loop assocd. with epithelial-fibroblastoid conversion and invasiveness

8/7/118 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

125189381 CA: 125(15)189381p PATENT
Multiple component RNA catalysts and their use in targeted cleavage of mRNA
INVENTOR(AUTHOR): Pyle, Anna M.; Michels, William J.
LOCATION: USA
ASSIGNEE: Trustees of Columbia University in the City of New York
PATENT: PCT International ; WO 9622689 A1 DATE: 960801
APPLICATION: WO 96US1337 (960125) *US 378235 (950125)
PAGES: 207 pp. CODEN: PIXXD2 LANGUAGE: English CLASS:
A01N-043/04A;
A01N-063/00B; A61K-031/70B; A61K-048/00B; C12N-001/00B;
C12N-005/00B;
C12N-005/06B; C12N-005/10B; C12N-015/00B; C12N-015/09B;
C12N-015/11B
DESIGNATED COUNTRIES: AU; CA; JP; MX; US DESIGNATED
REGIONAL: AT; BE; CH
; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA207004 Enzymes
IDENTIFIERS: group II intron multipartite kinetics mechanism, mRNA cleavage group II intron
DESCRIPTORS:
Gene,animal...
ets, mRNA for; multiple component RNA catalysts and their use in targeted cleavage of mRNA
Gene,animal...

fig, mRNA for; multiple component RNA catalysts and their use in
targeted cleavage of mRNA
Gene,animal...
gp55, mRNA for FSFV; multiple component RNA catalysts and their use in
targeted cleavage of mRNA
Genetic element,intron...
group II; multiple component RNA catalysts and their use in targeted
cleavage of mRNA
Recombination,genetic, translocation...
mRNA assocd. with; multiple component RNA catalysts and their use in
targeted cleavage of mRNA
Gene,microbial, tat...
mRNA for HIV; multiple component RNA catalysts and their use in
targeted cleavage of mRNA
Gene,microbial, early...
mRNA for JCV and LPV; multiple component RNA catalysts and their use
in
targeted cleavage of mRNA
Gene,microbial, tag...
mRNA for SV40; multiple component RNA catalysts and their use in
targeted cleavage of mRNA
Animal growth regulators... Animal growth regulators,angiogenic factors...
Animal growth regulators,transforming growth factors... Animal growth
regulators,.alpha.-transforming growth factors... Animal growth
regulators,.beta.-transforming growth factors... G proteins(guanine
nucleotide-binding proteins)... Gene,animal, anti-onco-... Gene,animal,
bcl-2... Gene,animal, bcr-c-abl... Gene,animal, bek... Gene,animal, c-abl
... Gene,animal, c-erbA... Gene,animal, c-erbB... Gene,animal, c-erbB2...
Gene,animal, c-fes... Gene,animal, c-fms... Gene,animal, c-fos...
Gene,animal, c-Ha-ras... Gene,animal, c-kit... Gene,animal, c-mos...
Gene,animal, c-myb... Gene,animal, c-myc... Gene,animal, c-ras...
Gene,animal, c-sea... Gene,animal, DCC... Gene,animal, Jun... Gene,animal,
lck... Gene,animal, L-myc... Gene,animal, met... Gene,animal, NF1...
Gene,animal, N-myc... Gene,animal, N-ras... Gene,animal, onco-...
Gene,animal, pim-1... Gene,animal, RB1... Gene,animal, rel... Gene,animal,
Tgf-.beta.... Gene,animal, TP53... Gene,animal, trk... Gene,animal, trkB...
Gene,animal, WT1... Gene,microbial, onco-... Gene,microbial, v-abl...
Gene,microbial, v-Ha-ras... Gene,microbial, v-jun...
Glycophosphoproteins,CFTR (cystic fibrosis transmembrane conductance
regulator)... Glycophosphoproteins,P-, gene mdr1... Gonadotropin receptors
... Interferons... Lymphokine and cytokine receptors,interleukin 1...
Lymphokine and cytokine receptors,interleukin 2... Lymphokines and
Cytokines,interleukin 1... Lymphokines and Cytokines,interleukin 2...
Lymphokines and Cytokines,interleukin 4... Lymphokines and
Cytokines,interleukin 6... Lymphokines and Cytokines,interleukins...
Lymphokines and Cytokines,scatter factor... Lymphokines and
Cytokines,tumor
necrosis factor... Receptors,gonadotropin... Receptors,interleukin 1...
Receptors,interleukin 2...
mRNA for; multiple component RNA catalysts and their use in targeted
cleavage of mRNA
Gene,microbial...
mRNA of bovine papilloma virus; multiple component RNA catalysts and
their use in targeted cleavage of mRNA
Alfalfa... Apple... Asparagus... Bacteria... Banana... Brassica,mustard...
Broccoli... Cabbage... Carrot... Celery... Chicory... Coffee(Coffea)...
Corn... Cottonseed... Cucumber... Cucurbita,squash... Grape... Lettuce...
Mammal... Melon(plant),cantaloupe... Palmae... Plant... Potato...
Rape(plant)... Raspberry... Soybean... Strawberry... Sunflower... Tomato...
Virus... Virus,animal, cytomegalo-... Virus,animal, Epstein-Barr...
Virus,animal, hepatitis B... Virus,animal, hepatitis C... Virus,animal,
herpes... Virus,animal, human immunodeficiency 1... Virus,animal, human
T-cell leukemia... Virus,animal, immunodeficiency... Virus,animal,
influenza... Virus,animal, papilloma... Virus,animal, picorna-...
Virus,animal, polio-... Wheat... Yeast...
mRNA of; multiple component RNA catalysts and their use in targeted
cleavage of mRNA
Animal cell line,CHO... Animal cell line,COS... Escherichia coli...
multipartite ribozyme-encoding vector-contg.; multiple component RNA
catalysts and their use in targeted cleavage of mRNA
Cations,divalent... Ribonucleic acids,messenger... Ribozymes...
multiple component RNA catalysts and their use in targeted cleavage of
mRNA
Gene,animal...
PY mTag, mRNA for; multiple component RNA catalysts and their use in
targeted cleavage of mRNA
Gene,animal...
retinoblastoma-1, mRNA for; multiple component RNA catalysts and their
use in targeted cleavage of mRNA
Gene,animal...
TGF-.alpha., mRNA for; multiple component RNA catalysts and their use
in targeted cleavage of mRNA
Canis familiaris... Cattle... Chicken... Felis catus... Fish... Goat...
Horse... Rodent... Sheep... Swine... Turkey...
transgenic, multipartite ribozyme-producing; multiple component RNA
catalysts and their use in targeted cleavage of mRNA
CAS REGISTRY NUMBERS:
16397-91-4 22537-22-0 biological studies, multiple component RNA
catalysts and their use in targeted cleavage of mRNA
9002-72-6 9061-61-4 11096-26-7 61912-98-9 62031-54-3 62229-50-9
67763-96-6 81627-83-0 83869-56-1 106096-93-9 148348-15-6
mRNA for;
multiple component RNA catalysts and their use in targeted cleavage of
mRNA

8/7/119 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

125084098 CA: 125(7)84098y CONFERENCE PROCEEDING
Phage antibodies against HGF/SF and other kringle-containing proteins
AUTHOR(S): Zaccolo, M.; Prospero, T. D.; Griffiths, A.; Winter, G.;
Gherardi, E.
LOCATION: ICRF Cell Interactions Laboratory, Centre Protein
Engineering,
Cambridge, UK,
JOURNAL: Perspect. Protein Eng. Complementary Technol., Collect. Pap.,
Int. Symp., 3rd EDITOR: Geisow, Michael J. (Ed), Epton, Roger (Ed),
DATE: 1995 PAGES: 170-171 CODEN: 62ZQAP LANGUAGE: English
MEETING DATE: 940000 PUBLISHER: Mayflower
Worldwide,Kingswinford, UK
SECTION:
CA215003 Immunochemistry
CA202XXX Mammalian Hormones
IDENTIFIERS: phage library antibody hepatocyte growth factor, kringle
contg protein phage library antibody
DESCRIPTORS:
Antibodies... Combinatorial library... Gene,animal... Lymphokines and
Cytokines,scatter factor... Proteins,specific or class,
macrophage-stimulating... Virus,bacterial...
phage human antibodies to hepatocyte growth factor/scatter factor and
other kringle-contg. proteins
CAS REGISTRY NUMBERS:
9001-90-5 139639-23-9 139639-24-0 phage human antibodies to
hepatocyte
growth factor/scatter factor and other kringle-contg. proteins

8/7/120 (Item 7 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

125000714 CA: 125(1)714k CONFERENCE PROCEEDING
Effects of cyclosporine on experimental liver carcinogenesis
AUTHOR(S): Shinozuka, H.; Kubo, Y.; Katyal, S. L.
LOCATION: School Medicine, University Pittsburgh, Pittsburgh, PA, USA
JOURNAL: Proc. Int. Cancer Congr., Free Pap. Posters, 16th EDITOR: Rao,
R. S (Ed), DATE: 1994 VOLUME: 3, PAGES: 1939-1943 CODEN: 62UYAO
LANGUAGE: English PUBLISHER: Monduzzi Editore,Bologna, Italy
SECTION:
CA201006 Pharmacology
CA215XXX Immunochemistry
IDENTIFIERS: cyclosporine liver carcinogenesis
DESCRIPTORS:
Lipopolysaccharides...
bacterial; effects of cyclosporine on exptl. liver carcinogenesis
Animal growth regulators,.alpha.-transforming growth factors... Animal
growth regulators,.beta.1-transforming growth factors... Cell proliferation
... Liver,neoplasm, hepatoma... Liver,neoplasm, hepatoma, inhibitors...
Lymphokines and Cytokines,scatter factor... Neoplasm inhibitors,hepatoma...
Ribonucleic acids,messenger...

effects of cyclosporine on exptl. liver carcinogenesis
CAS REGISTRY NUMBERS:
59865-13-3 effects of cyclosporine on exptl. liver carcinogenesis

8/7/121 (Item 8 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

123195440 CA: 123(15)195440g JOURNAL
Hepatic nitric oxide production following acute endotoxemia in rats is mediated by increased inducible nitric oxide synthase gene expression
AUTHOR(S): Laskin, Debra L.; Valle, Marina Rodriguez Del; Heck, Diane E.; Hwang, Shaw-Min; Ohnishi, S. Tsuyoshi; Durham, Stephen K.; Goller, Nancy L.
; Laskin, Jeffrey D.
LOCATION: Environmental and Occupational Health Sciences Institute, Rutgers University, Piscataway, NJ, 08855-0789, USA
JOURNAL: Hepatology (Philadelphia) DATE: 1995 VOLUME: 22 NUMBER: 1
PAGES: 223-34 CODEN: HPTLD9 ISSN: 0270-9139 LANGUAGE: English
SECTION:
CA214003 Mammalian Pathological Biochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: nitric oxide formation liver endotoxemia
DESCRIPTORS:
Animal growth regulators... Interferons,.gamma.... Liver,hepatocyte...
Lymphokines and Cytokines,scatter factor... Lymphokines and Cytokines,tumor
necrosis factor... Sepsis and Septicemia,endotoxemia...
hepatic nitric oxide formation may contribute to the pathophysiol. of acute endotoxemia
Apoptosis...
inhibition, hepatocyte; hepatic nitric oxide formation may contribute to the pathophysiol. of acute endotoxemia
Cell proliferation... Translation,genetic...
inhibition; hepatic nitric oxide formation may contribute to the pathophysiol. of acute endotoxemia
Gene,animal...
nitric oxide synthase; hepatic nitric oxide formation may contribute to the pathophysiol. of acute endotoxemia
CAS REGISTRY NUMBERS:
10102-43-9 biological studies, hepatic nitric oxide formation may contribute to the pathophysiol. of acute endotoxemia
81627-83-0 83869-56-1 125978-95-2 hepatic nitric oxide formation may contribute to the pathophysiol. of acute endotoxemia

8/7/122 (Item 9 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

120317359 CA: 120(25)317359y PATENT
Regulation of gene transcription by ionizing radiation and its applications
INVENTOR(AUTHOR): Weichselbaum, Ralph R.; Hallahan, Dennis E.; Sukhatme,
Vikas P.; Kufe, Donald W.
LOCATION: USA
ASSIGNEE: Arch Development Corp.
PATENT: PCT International ; WO 9406916 A1 DATE: 940331
APPLICATION: WO 93US8432 (930908) *US 943812 (920911)
PAGES: 101 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-015/67A;
C12N-015/62B; C12N-015/85B; A61K-031/70B; A61K-041/00B
DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE; CH; DE; DK
; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA203004 Biochemical Genetics
CA201XXX Pharmacology
IDENTIFIERS: ionizing radiation gene transcription activation, enhancer promoter radiation activation, tumor therapy radiation TNF expression
DESCRIPTORS:
Gene,animal, anti-onco-...
expression of, regulation by radiation-responsive enhancer-promoter of
Gene,animal, JE...
expression of, regulation by radiation-responsive enhancer-promoterof of
Neoplasm inhibitors...
gene for, expression of, radiation-responsive enhancer-promoterof for
Histocompatibility antigens,HLA-A... Histocompatibility antigens,HLA-B...
Histocompatibility antigens,HLA-C... Histocompatibility antigens,MHC (major histocompatibility complex)... Lymphokines and Cytokines...
gene for, expression of, regulation by radiation-responsive enhancer-promoter of
Animal growth regulators... Animal growth regulators,blood platelet-derived growth factors... Animal growth regulators,receptors... Animal growth regulators,smooth muscle cell-derived growth factors... Anticoagulants and Antithrombotics... Eye,neoplasm, retinoblastoma...
Hemopoietins,hematopoietic cell growth factors... Kidney,neoplasm, Wilms'
... Lymphokines and Cytokines,interleukin 1... Lymphokines and Cytokines,interleukin 3... Lymphokines and Cytokines,interleukin 4...
Lymphokines and Cytokines,interleukin 6... Lymphokines and Cytokines,scatter factor... Receptors,animal growth regulator...
Thrombolytics...
gene for, expression of, regulation by radiation-responsive enhancer-promoterof of
Proteins,specific or class, DNA-binding...
gene for, in DNA construct for radiation-responsive expression of polypeptide
Ribonucleic acid formation factors,NF-.kappa.B (nuclear factor .kappa.B)...
Ribonucleic acid formation factors,Vmw65 (virion-assocd. stimulatory protein, 65,000-mol.-wt.)...
gene for, in DNA construct for radiation-responsive gene expression
Kidney,composition...
growth factor, gene for, expression of, regulation by radiation-responsive enhancer-promoterof of
Gene,microbial, GAL4...
in DNA construct for radiation-responsive gene expression
Blood vessel,composition...
inhibitor for, expression of, regulation by radiation-responsive enhancer-promoter of
Gene,animal, c-jun... Gene,animal, Egr-1... Lymphokines and Cytokines,tumor necrosis factor-.alpha....
promoter of, radiation-responsive, gene transcription activation by
Toxins...
Pseudomonas, expression of, regulation by radiation-responsive enhancer-promoterof of
Genetic element,enhancer element... Genetic element,promoter...
radiation-responsive, gene transcription regulated by
CAS REGISTRY NUMBERS:
9002-01-1 9002-06-6 9025-05-2 9054-89-1 62683-29-8 81627-83-0 83869-56-1 105844-41-5 105913-11-9 106096-92-8 106096-93-9 130996-27-9 143011-72-7 gene for, expression of, regulation by radiation-responsive enhancer-promoterof of
9002-72-6 gene for, of human, transcription terminator of, in DNA construct for radiation-responsive gene expression

8/7/123 (Item 10 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

119112926 CA: 119(11)112926p PATENT
Method using DNA or RNA labels and PCR for the detection or quantitation of trace substances
INVENTOR(AUTHOR): Sasaki, Kazuyuki; Sato, Takeya
LOCATION: Japan,
ASSIGNEE: Nisshin Flour Milling Co., Ltd.
PATENT: European Pat. Appl. ; EP 544212 A1 DATE: 930602
APPLICATION: EP 92119952 (921124) *JP 91335580 (911126)
PAGES: 11 pp. CODEN: EPXXDW LANGUAGE: English CLASS: C12Q-001/68A;
G01N-033/58B DESIGNATED COUNTRIES: CH; DE; FR; GB; LI; SE
SECTION:
CA209002 Biochemical Methods
CA202XXX Mammalian Hormones
CA203XXX Biochemical Genetics
IDENTIFIERS: trace substance DNA label PCR
DESCRIPTORS:
Toxins...

bacterial, detn. of trace amt. of, method using DNA label and PCR for
Neoplasm...
detn. of trace amt. of marker of, method using DNA label and PCR for
Animal growth regulators... Animal growth regulators,blood platelet-derived growth factors... Animal growth regulators,fibroblast growth regulatory factors... Antibodies... Antibodies,auto-... Antigens... Blood-coagulation factors... Enzymes... Hormones... Lipoproteins... Lymphokines and Cytokines,scatter factor... Organic compounds,biol.,analysis... Proteins,specific or class, C-reactive... Receptors...
detn. of trace amt. of, method using DNA label and PCR for
Virion structure,capsid...
detn. of trace components of, method using DNA label and PCR for
Digestive tract...
detn. of trace hormones of, method using DNA label and PCR for
Spore...
exosporium, detn. of trace components of, method using DNA label and PCR for
Nucleic acids...
label, method using PCR and, for trace substance detn.
Deoxyribonucleic acids... Ribonucleic acids...
measurement of, in method using nucleic acid label and PCR, for trace substance detn.
Bacteria...
metabolites of, detn. of trace amt. of, method using DNA label and PCR for
Polymerase chain reaction...
method using DNA label and, for detn. of trace substance
CAS REGISTRY NUMBERS:
9002-60-2 9004-10-8 analysis, detn. of trace amt. of, method using DNA label and PCR for
149408-56-0 as primer, for prepg. biotinylated label DNA, in method using DNA-labeled antibody and PCR, for glicentin detn.
149408-54-8 149408-55-9 as primer, in method using DNA-labeled antibody and PCR, for glicentin detn.
9000-86-6 9000-97-9 9001-60-9 9001-78-9 9002-67-9 9002-71-5 9002-72-6 9061-61-4 61912-98-9 62229-50-9 71567-77-6 detn. of trace amt. of, method using DNA label and PCR for
9012-90-2 9014-24-8 in anal. method using DNA label and PCR, for detn. of trace substance such as hormone and etc.
35013-72-0 reaction of, in prepn. of biotinylated label DNA, in method using DNA-labeled antibody and PCR, for glicentin detn.
149408-53-7D thio-linked, anti-glicentin antibody labeled with, in method using DNA label and PCR, for glicentin detn.

8/7/124 (Item 11 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

117144419 CA: 117(15)144419a JOURNAL
Molecular biological studies on gene induced by non-A non-B hepatitis virus infection
AUTHOR(S): Kitamura, Naomi
LOCATION: Inst. Liver. Res., Kansai Med. Univ., Moriguchi, Japan, 570
JOURNAL: Yakugaku Kenkyu no Shinpo DATE: 1992 VOLUME: 8, PAGES: 111-25
CODEN: YAKSEY ISSN: 0914-4544 LANGUAGE: Japanese
SECTION:
CA203000 Biochemical Genetics
CA214XXX Mammalian Pathological Biochemistry
IDENTIFIERS: hepatitis C virus infection protein review, p44 protein gene HCV infection review, promoter p44 protein HCV infection review
DESCRIPTORS:
Gene,animal...
for p44 protein, hepatitis C virus infection induction in relation to
Lymphokines and Cytokines,scatter factor...
gene for, structure and promoter and activation of
Proteins,specific or class, p44...
hepatitis C virus infection induction of
Genetic element...
ISRE (interferon stimulated-responsive element), of protein p44 gene of human and chimpanzee
Virus,animal, hepatitis C...
p44 protein gene induced by infection with, characterization of

8/7/125 (Item 12 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

112153444 CA: 112(17)153444d JOURNAL
Suppression by morphine and ethanol of tumor cell cytotoxic activity released by macrophages from retrovirally infected mice upon in vitro stimulation by beta carotene
AUTHOR(S): Watson, Ronald R.; Nguyen, Tuan H.
LOCATION: Sch. Med., Univ. Arizona, Tucson, AZ, 85724, USA
JOURNAL: Prog. Clin. Biol. Res. DATE: 1990 VOLUME: 325 NUMBER: Alcohol, Immunomodulation, AIDS PAGES: 79-91 CODEN: PCBRD2 ISSN: 0361-7742 LANGUAGE: English MEETING DATE: 890000
SECTION:
CA204006 Toxicology
CA214XXX Mammalian Pathological Biochemistry
CA218XXX Animal Nutrition
IDENTIFIERS: carotene macrophages tumor cytotoxicity morphine ethanol, retrovirus carotene macrophage tumor cytotoxicity
DESCRIPTORS:
Virus,animal, murine leukemia LP-BM5...
morphine effect on tumor cytotoxic factor prodn. by carotene-stimulated macrophages in relation to
Lymphokines and Cytokines,tumor necrosis factor...
of macrophages and human monocytes, carotene effect on, morphine in relation to
Macrophage...
tumor cytotoxic factor of, carotene effect on, morphine in relation to
Monocyte...
tumor cytotoxic factor of human, carotene effect on, morphine in relation to
CAS REGISTRY NUMBERS:
57-27-2 biological studies, carotene effect on tumor cytotoxic factor of macrophages and human monocytes response to
64-17-5 biological studies, tumor cytotoxic factor prodn. by carotene-stimulated and retro virus-infected macrophages in relation to
7235-40-7 tumor cytotoxic factor of macrophages and human monocytes response to, morphine in relation to
79-81-2 tumor cytotoxic factor prodn. by carotene-stimulated and retro virus-infected macrophages in relation to

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Set   Items  Description
S1    16300  (SCATTER(W)FACTOR? OR
TUMOR(W)CYTOTOXIC(W)FACOR? OR TCF OR
       TCF(W)II)
S2       12  S1 AND SEPSIS AND (TREAT? OR PREVENT? OR MODULAT?
OR REDUC?
         OR AMELORIAT?)
S3       12  RD S2 (unique items)
S4     8974  (SCATTER(W)FACTOR? OR
TUMOR(W)CYTOTOXIC(W)FACOR? OR TCF(W)-
       II)
S5     9070  (SCATTER(W)FACTOR? OR
TUMOR(W)CYTOTOXIC(W)FACTOR? OR TCF(W-
       )II)
S6      301  S5 AND (SEPSIS OR INFECT? OR MICROB? OR BACTER?)
S7      198  RD S6 (unique items)
S8      125  S7 AND PY<2000
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    09apr02 09:21:16 User226352 Session D618.3
       $9.58   1.711 DialUnits File5
         $43.75  25 Type(s) in Format  7
       $43.75  25 Types
   $53.33  Estimated cost File5
       $1.79   0.304 DialUnits File6
    $1.79  Estimated cost File6
       $24.94   1.459 DialUnits File34
         $67.90  14 Type(s) in Format  7
         $21.00  5 Type(s) in Format 14
         $46.20  11 Type(s) in Format 15
       $135.10  30 Types
   $160.04  Estimated cost File34
       $0.75   0.108 DialUnits File40
    $0.75  Estimated cost File40
       $0.70   0.146 DialUnits File41
    $0.70  Estimated cost File41
       $4.24   0.941 DialUnits File50
    $4.24  Estimated cost File50
       $1.34   0.358 DialUnits File65
    $1.34  Estimated cost File65
       $0.40   0.167 DialUnits File68
    $0.40  Estimated cost File68
       $5.44   0.755 DialUnits File71
         $12.80  8 Type(s) in Format  7
       $12.80  8 Types
    $18.24  Estimated cost File71
       $26.36   2.929 DialUnits File73
         $150.00  60 Type(s) in Format  7
       $150.00  60 Types
   $176.36  Estimated cost File73
       $4.02   0.789 DialUnits File76
    $4.02  Estimated cost File76
       $0.29   0.100 DialUnits File77
    $0.29  Estimated cost File77
       $4.13   1.180 DialUnits File94
    $4.13  Estimated cost File94
       $3.95   1.648 DialUnits File98
         $10.05  3 Type(s) in Format  7
       $10.05  3 Types
    $14.00  Estimated cost File98
       $2.93   0.575 DialUnits File103
         $1.65  1 Type(s) in Format  7
       $1.65  1 Types
    $4.58  Estimated cost File103
       $0.42   0.177 DialUnits File143
    $0.42  Estimated cost File143
       $6.31   1.803 DialUnits File144
         $1.65  1 Type(s) in Format  7
       $1.65  1 Types
    $7.96  Estimated cost File144
       $6.70   2.093 DialUnits File155
         $0.42  2 Type(s) in Format  7
       $0.42  2 Types
    $7.12  Estimated cost File155
       $1.93   0.714 DialUnits File156
    $1.93  Estimated cost File156
       $1.51   0.335 DialUnits File162
    $1.51  Estimated cost File162
       $0.75   0.084 DialUnits File172
    $0.75  Estimated cost File172
       $1.11   0.143 DialUnits File305
    $1.11  Estimated cost File305
       $0.26   0.076 DialUnits File369
    $0.26  Estimated cost File369
       $0.32   0.092 DialUnits File370
    $0.32  Estimated cost File370
       $29.48   2.349 DialUnits File399
         $33.00  12 Type(s) in Format  7
       $33.00  12 Types
    $62.48  Estimated cost File399
       $11.76   0.687 DialUnits File434
    $11.76  Estimated cost File434
       OneSearch, 26 files, 21.724 DialUnits FileOS
    $3.68  TELNET
   $543.51  Estimated cost this search
   $543.52  Estimated total session cost  22.086 DialUnits
Logoff: level 02.03.27 D  09:21:16
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